Clinical Features of Diabetic Acidosis and Coma

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Acidosis is a reduction of alkali reserve of the blood, an acidemia due to an excess accumulation of acid metabolites. It is more the natural result of uncontrolled severe diabetes than it is a complication of this disease. As Guest[1] has emphasized, its development "is always initiated by insulin insufficiency regardless of the mechanism responsible for an increased need."

PATHOLOGIC PHYSIOLOGY

The associated events which lead to this condition are in part concurrent, but are in a constant state of change. To simplify this extremely complex chain of events into terms more readily applicable at the clinical level, we may speak of them as occurring in the following phases:

(1) Hyperglycemia occurs, producing glycosuria, which, when extreme, causes severe polyuria and dehydration.

(2) Glycogen depletion occurs, which is extreme in the liver, very slight in the skeletal muscle, and negligible or absent in the heart.

(3) Muscle breakdown occurs, resulting in increased excretion of urinary nitrogen and aggravating the already high phosphorus loss.

(4) Excess quantities of ketone bodies are formed. These metabolites are chiefly from fat and formed almost entirely in the liver, but perhaps somewhat in adipose tissue. This is a normal process which becomes abnormal when the rate of production increases excessively. Tremendous quantities of urinary ketones sometimes exceeding 100 gm. per day are recorded.[3] Three substances are especially involved. These are usually listed as *B*-hydroxybutyric acid, aceto-acetic acid and acetone, known collectively as ketone bodies. Aceto-acetic (diacetic) acid is particularly toxic. The body is incapable of oxidizing these substances above a certain limit. Beyond this limit they accumulate in the blood and tissues.

(5) Electrolytes, especially sodium and alkali, are lost in the urine with the excretion of acid metabolites.

(6) The alkali reserve of the blood falls, as reflected by the diminishing power of the blood to combine with carbon dioxide. Finally the *p*H of the blood decreases. The level of the total base commonly falls from a normal of 155 mEq/L to between 135 and 145.

(7) The level of blood fats rises; neutral fat may be extremely high and lipemia may be easily seen grossly. The blood cholesterol level is often elevated sometimes to 800 or 900 mg. per 100 cc. and occasionally to twice that level. High total blood fat may be associated with low cholesterol levels in the presence of infection. Lipoproteins are increased in the blood and the Tiselius protein pattern shows a high peak of beta and gamma globulins. In my experience, such changes as those in blood protein and fat have no clinical importance either in the prognosis or treatment of ketosis.

The exact role played by each of many factors in the production of the clinical symptoms and signs of acidosis has not been determined, but the consensus seems to be that among the most important are: 1) the direct toxic effect of ketone bodies upon the cells; and 2) dehydration. Other causes are loss of electrolytes, with loss of alkali reserves and the diminished rate of oxygen utilization by the brain. Hyperglycemia in itself appears to be relatively unimportant.

TERMS

The term "ketosis" is employed when ketone bodies have risen in urine and/or blood to abnormal levels, regardless of changes in alkali reserve. The term

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"acidosis" should be reserved for the state reached when ketosis has produced a fall in carbon dioxide combining power. The term "coma" properly means unconsciousness. There is little correlation between the degree of stupor and chemical findings such as blood sugar and carbon dioxide. One patient may be alert and even excited with a carbon dioxide combining power of 9, and another may be in deep stupor with a level of over 20 volumes. However, these examples are extreme. Generally speaking, severe symptoms are not present when the carbon dioxide combining power is 30 or above, but when below 15, severe symptoms are likely to exist. The validity of using the word "coma" in designating a state in which no stupor exists is controversial. Some clinicians object to it strenously. Others feel it is desirable to speak of coma in any case in which the carbon dioxide combining power is 25 or below and still others specify 20 or below. Root[13] feels that he is fully justified in using the term in cases with the lower carbon dioxide levels mentioned because it is an advantage in grouping cases for study, and it serves to call attention to the serious nature of the impending condition, though drowsiness does not exist. In addition he points out that in pre-insulin days patients in diabetic acidosis with a level of carbon dioxide below 20 almost never recovered.

There is a much closer parallelism between the concentration of ketone bodies in the blood and the degree of coma[2] although even this correlation is sometimes extremely poor. Patients have been reported mentally alert with a total blood ketone level of 123 mg. per 100 cc. as acetone and another unconscious with a level of 18.[4] The patient, however, usually becomes drowsy when the total ketone level reaches more than 60 mg. per 100 cc. and unconscious when it exceeds 100.

In considering the importance of various factors, Fisher[4] has called attention to the fact that experimentally ketone bodies cause death only when given in hypertonic solution. On the other hand Kety[14] has demonstrated that there is a striking fall in the rate of oxygen consumption by the brain in diabetic acidosis and when it falls from a normal 3.5 cc. per 100 gm. per minute to 2.1 cc., unconsciousness invariably results.

FREQUENCY

The frequency of diabetic ketosis is not known but it is certainly extremely common. Ketonuria may be detected in most diabetic patients at one time or another if they are closely followed and this is especially true in children. It is only when there is a serious acute complication that it is likely to be accompanied by symptoms. Before insulin was available for treatment, diabetic coma accounted for more than 40 per cent of deaths of all diabetic patients, but it now accounts for less than 2 per cent.

MORTALITY

The mortality rate of coma itself has been greatly reduced, but in many places it is still high. For patients in actual coma reduction of the rate to 10 per cent has probably been attained by few; apparently much higher mortality rates, from 25 to 40 per cent, still exist. A great deal can be accomplished by intensive effort and well-organized teamwork. For example, Harwood in discussing Howard's paper[5] at the 1950 American Diabetes Association meeting, stated that the mortality rate for diabetic coma had been 10 to 25 per cent at the Massachusetts General Hospital for years. Late in 1944, an effort was made to try to match the mortality rate of less than 5 per cent achieved by Joslin's group. Since that time he reported only one death in 70 cases and that was from uremia in the case of a 75 year old woman, four days after acidosis had been controlled.

ONSET

The rate at which symptoms arise may be rapid or very slow. The onset, especially in a child, may come in a few hours, no symptoms being recognized until vomiting and stupor suddenly appear and the situation is found to be critical. At the other extreme, an individual may struggle to carry on his work in spite of weakness, weight loss and severe polyuria for a year, presenting no change in symptoms over a period of weeks, and then be found to have acidosis with a carbon dioxide combining power below 20 volumes per 100 cc.

PRECIPITATING FACTORS

The factors precipitating acidosis vary greatly, but the variations are similar in the experience of physicians who see many diabetic patients. Severe symptoms may appear to be precipitated by pregnancy; a surgical operation; hyperthyroidism; or many types of stress or injury.

Infections of varied types may be responsible. Among 50 consecutive cases diagnosed as acidosis requiring hospital care, we found the common cold; bronchitis; broncho-pneumonia; otitis media; sore throat; thrush; periapical dental abscess; carbuncle; boil; cellulitis; paronychia; cholecystitis; and meningitis.

Unfortunately, there are still many patients entering our hospitals with diabetic coma with unrecognized and

untreated diabetes. It is equally tragic to find that a large number face this serious crisis because of omission of insulin treatment. This is a common error: the patient having omitted his meals because of illness concludes that he should omit his insulin not realizing that his need for it is greater than ever.

PREVENTION

The treatment of diabetic acidosis begins with prevention and this obviously entails detection and education; it also necessitates continued supervision. With regard to detection, I recommend the routine use of the blood sugar test. If blood sugar tests were done routinely by internists in all new cases, diabetes now frequently overlooked would be recognized.

By the use of routine blood sugar tests at the Cleveland Clinic, diabetes is found in 4.0 per cent of our patients. Only 2.4 per cent of the same group would be recognized to have the disease if history, symptoms and urinalysis alone were depended upon for the diagnosis.[11] We have found that routine blood sugar tests on all surgical patients have virtually eliminated acidosis postoperatively.

It is unnecessary to mention here that education of the patient is paramount: He should always continue his urine tests when an intercurrent illness supervenes, should never discontinue the use of insulin when glycosuria is present, and should promptly report loss of control of glycosuria, the appearance of ketonuria, or the occurrence of infection.

SYMPTOMATOLOGY

The symptoms of acidosis may be superimposed upon cardinal symptoms of diabetes or may appear suddenly. They may be extremely mild or exceedingly severe. With a steadily falling alkali reserve common symptoms are: Increased weakness, lassitude, and unusual need for rest; increased dyspnea on exertion; loss of appetite merging with actual nausea and vomiting; air hunger; headache; generalized aches and pains; dryness of the skin, mouth and throat; fever; and abdominal pain. The urine contains not only sugar and diacetic acid, but often albumin and casts.

If the condition is more severe the patient presents a picture of prostration, dehydration, flushing of the cheeks, rapid deep breathing, and acetone odor of the breath. He may have coffee ground vomitus. Thirst is incessant and somnolence of various degrees is seen. The eyeballs are soft. A temperature of 102° or 103° F. is common, due in part to dehydration and often aggravated by an accompanying infection. The nausea, vomiting, and abdominal pain tend to subside as stupor increases. Most patients, even in relatively severe acidosis, can be aroused.

The abdominal pain may be severe and occasionally may simulate pancreatitis, appendicitis or other intra-abdominal infection. Intra-abdominal infection may exist concurrently and be a precipitating factor. Usually, however, an hour or two of active treatment will completely relieve pain if it is due to acidosis. Leukocytosis well over 25,000 with a high neutrophil count is common with acidosis without infection, and this may make the differential diagnosis of an acute abdominal emergency a matter of concern for several hours. The sedimentation rate is also high in acidosis uncomplicated by infection.

Weakness of the respiratory muscles is often seen in severe coma. Distention of the stomach and colon may be present. The possibility of anuria should be considered.

ESTIMATION OF THE PROGNOSIS

In acidosis which is severe or prolonged, clinical evaluation is of great importance. This includes: an estimate of the degree of coma; its duration; consideration of the age of the patient; the severity of infection, if present; and, especially, a careful estimate of the cardiovascular system. The events leading to death in many cases indicate cardiac collapse with relatively acute failure often closely following falling blood pressure and evidence of peripheral vascular failure with the picture of shock. The severity index of Rabinowitch[6] may be used to considerable advantage.

INSULIN RESISTANCE

The clinician should be on the alert for insulin resistance. A need for several thousand units in the first 12 to 24 hours is not uncommon. Such relative resistance may be intimately associated with the acidosis, and the requirements may diminish to average levels rapidly. On the other hand acidosis may be controlled with 200 units per day; subsequently, more than 1000 units may be necessary, such high requirements diminishing when existing infection is brought under control. This situation is illustrated in Figure 1.

DIAGNOSIS

The diagnosis is usually not difficult. If a history of diabetes is present; if a reasonable number of the typi-

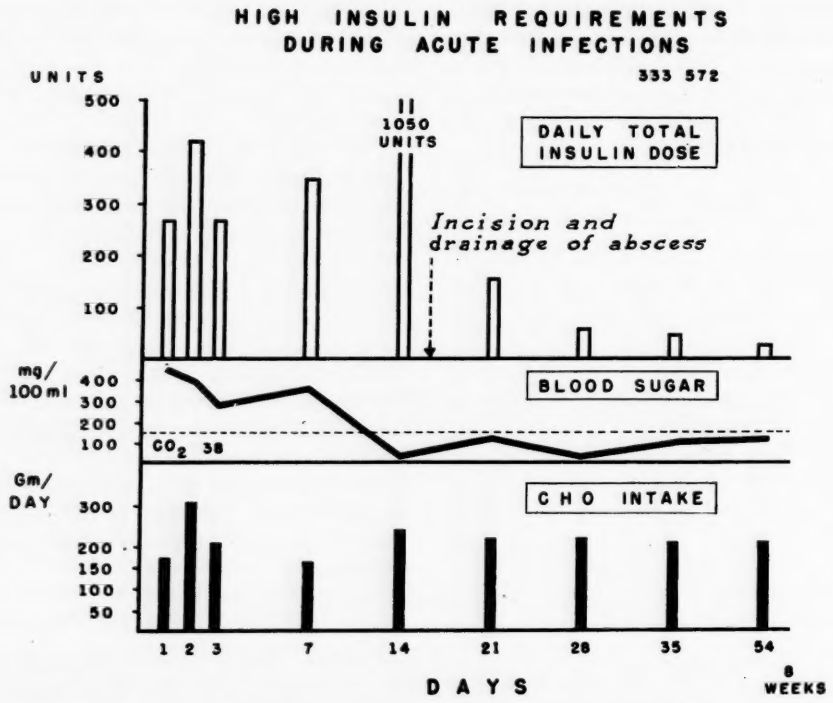

FIGURE 1. Marked insulin resistance associated with infection. The mild acidosis disappeared under treatment within a day and an abscess was drained.

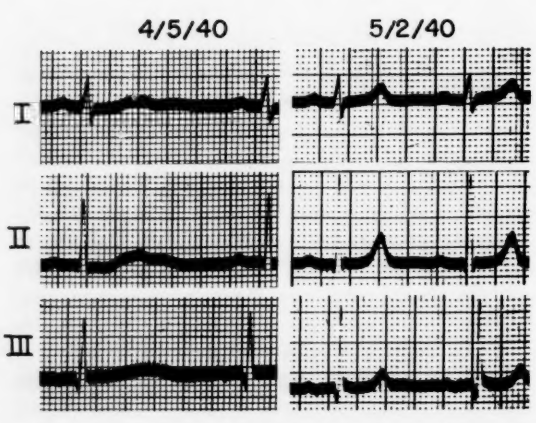

FIGURE 2. Hypopotassemia due to overtreatment with desoxycorticosterone acetate. The serum potassium content was 1.4 mEq/L on 4-5-40 and 4.1 mEq/L on 5-2-40. Prolonged Q-T interval, long flat T waves and U waves are present in the electrocardiogram on the left.

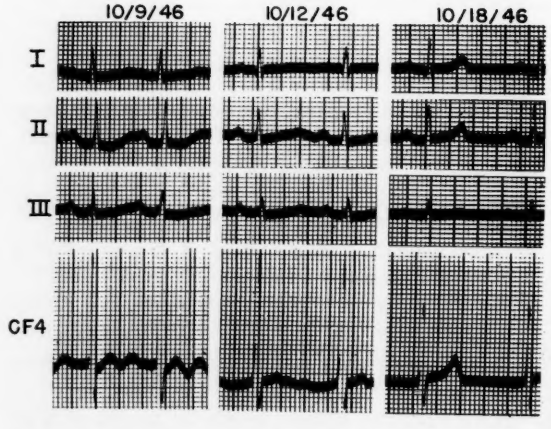

FIGURE 3. Hypopotassemia during and after diabetic acidosis. On 10-9-46 CO_2 combining power was 11.8. Serum potassium was as follows: 10-9-46—2.2; 10-12-46—2.7; and 10-18-46—5.4. Outstanding changes include low broad T waves, prolonged Q-T intervals and U waves, which are shown with particular clarity in lead CF4.

cal signs are evident; and if the urine contains a great deal of sugar and diacetic acid, the diagnosis is usually definite enough to warrant beginning treatment at once. This much evidence is necessary, but delay in therapy while waiting for extensive laboratory tests may be disastrous. In an unconscious patient with no friends or relatives to give a history, the matter is not nearly so simple.

If there is doubt, it is well to consider a number of other conditions which may be causing stupor or which may exist concurrently. These include: hypoglycemic shock; uremia; intoxication due to alcohol or drugs; shock due to trauma or hemorrhage; and also at times a number of cerebral disorders including trauma; vascular accidents; inflammation or brain tumor.

LABORATORY STUDIES

The first laboratory procedure to be done is obviously to test the urine for sugar and ketone bodies. Ketonuria may appear in various states of intoxication or starvation when diabetes is not involved, but diabetic acidosis is not usually present if the urine does not contain readily measurable amounts of diacetic acid. However, this is not always true for if acidosis is accompanied by severe renal impairment the urine may contain little or no ketone bodies.

The carbon dioxide combining power and blood sugar level should be determined at once. One may expect the blood sugar to be over 300, more commonly 600 and sometimes even over 1000 mg. per 100 cc., or more. In our practice the carbon dioxide combining power is the most useful single test in evaluating the metabolic disturbance. It indicates how close the blood is to serious depletion of alkali. A rapid test for blood ketone bodies[7] is particularly valuable for several reasons: 1) It is a good indication of the severity of acidosis. 2) It can be done quickly at the bedside. 3) It will differentiate between those cases in which blood and urine ketones are low and those in which these substances may be low in the urine and relatively high in the blood. 4) It will help to separate diabetic acidosis from uremia. Recently a test for blood ketones was made in the case of a patient who was anuric for 15 days. The carbon dioxide combining power was 29 and blood urea was 243. The blood ketone test was negative.

It would be highly desirable to know the blood *p*H and this test may be available to more clinicians in the future.

In addition it is very useful to know the blood chloride level, as indirectly it gives a good indication of the sodium levels.

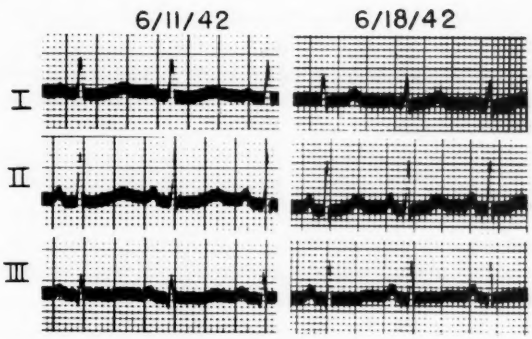

FIGURE 4. Hypopotassemia two days after beginning treatment for diabetic acidosis. CO_2 combining power was 9.0 on 6-9-42. Serum potassium mEq/L on 6-11-42 was 1.8 and on 6-19-42 was 4.1. Low rounded T waves and prolonged Q-T interval without U waves are shown in the first electrocardiogram.

A blood urea determination should be done. It may prove valuable to follow blood counts, especially if the original white cell count is elevated. Hematocrit levels will help determine hemoconcentration and should be followed serially. In diabetic acidosis it will give a reasonable estimate of blood volume.

SERUM POTASSIUM

In the past few years a great deal of attention has been given to the possible danger of low serum potassium. More complete knowledge of this subject is needed from the clinical standpoint. Several points, however, seem well established. Abnormally low serum potassium is relatively common in diabetic acidosis but usually appears after treatment is under way. In 82 cases studied by Martin[8] the serum potassium was below 2.9 mEq/L before treatment in 2 per cent of the patients. Within 48 hours after treatment was begun in the same group, the level was below 2.9 mEq/L in 14 per cent. It is well to remember that low serum potassium also may be present in chronic renal disease and may be produced by diarrhea, vomiting or constant gastric drainage.

The possibility of abnormally low serum potassium should be considered in all cases. It should be suspected where there is extreme muscle weakness, especially weakness of the diaphragm, or shock which does not respond well to usual therapy. It is commonly found where there has been a rapid fall in the blood sugar level, particularly when large amounts of fluids have been given intravenously. Hypotension; tachycardia; murmurs or cardiac dilatation; developing during the course of treatment[8] are possibly manifestations.

Changes in electrocardiograms typical of hypopotassemia are illustrated in Figure 2 (in a case in which there was overtreatment with desoxycorticosterone acetate) and in Figure 2 and 4 (cases of diabetic coma under treatment).

The earliest changes[9] due to hypopotassemia are rounding and broadening of the T-waves. Usually the T-waves are low in amplitude. The Q-T interval is prolonged depending entirely on the degree to which the duration of the T-waves is increased. Prominent U-waves are common. (In hypocalcemia. the Q-T interval is lengthened but the T-waves are normal, and U-waves do not appear.)

The level of serum potassium at which the electrocardiogram shows distinct changes is not well established. It appears to be approximately 2.5 mEq/L; and serious harm from hypopotassemia seems unlikely with levels above this range.

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New Knowledge Regarding Acidosis

The most important progress in the treatment of diabetic acidosis in recent years has stemmed from an improved understanding of the associated disturbances in the metabolism of water and electrolytes. Although it has long been recognized that diabetic acidosis is initiated by lack of insulin with a consequent inability of the body to utilize carbohydrates and an eventual profound depletion of salt and water, it has become increasingly apparent that even the most skillful correction of these defects does not save life in all cases, even in the absence of serious complicating illness.

From *Electrolyte Metabolism in Diabetic Acidosis,* by Randall G. Sprague, M.D. and Marschelle H. Power, Ph.D., in *The Journal* of the American Medical Association, March 1, 1953

Treatment of Diabetic Coma

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The basic principles in the treatment of diabetic coma are divided into two main parts. Immediate emergency treatment includes measures to restore carbohydrate metabolism to normal; to overcome dehydration; to eliminate ketosis; in extreme cases only, to combat acidosis specifically; and to treat precipitating factors, such as acute appendicitis, acute pyelitis and pyelonephritis. Management in the convalescent period demands watchfulness (for relapse and hidden infections), continued treatment of precipitating factors, and rapid nutritional rehabilitation with special reference to protein deficits and vitamin deficits.

FACTORS AFFECTING MORTALITY

The mortality rates from diabetic ketotic acidotic coma as reported in various large medical centers vary from one to 40 per cent depending on the age of the patient, the duration and intensity of the ketotic acidosis, precipitating and complicating diseases and the adequacy of the therapeutic procedures.

Delay in diagnosis and in the initiation of adequate treatment leads to many unnecessary fatalities. During the routine instruction of patients in their general care, they should be taught to recognize an impending decompensation of the diabetes and to treat the earliest stages rather than waiting for ketosis to develop.

Patients are instructed to test their urine for sugar every 4 hours during an episode of fever, vomiting, diarrhea, or very marked anorexia. They are further instructed to administer supplementary doses of regular insulin in accordance with prearranged scale. This prophylactic measure, it is felt, has saved many a patient from emergency hospitalization for ketotic acidosis. The supplementary insulin, over and above the daily scheduled dose, suppresses the glycosuria and polyuria, and thus prevents dehydration and loss of minerals; it enhances carbohydrate metabolism, thus preventing excessive ketone formation and accumulation. Very few well-instructed patients who cooperate ever develop an intense ketotic acidosis.

ADEQUATE THERAPY

It was stated in the introduction that the mortality rate depended upon the adequacy of the therapy. What is adequate therapy and how is it achieved?

From the metabolic point of view the first essential step is to restore carbohydrate metabolism. This in turn will stop the catabolic destruction of protein, allow orderly and normal fat metabolism, reduce the rate of ketone body formation, and allow for the metabolism of the already existing excess of ketones. For this purpose, the essential therapeutic agent is insulin, meaning the water soluble regular insulin or the solution of insulin crystals with its comparatively short period of latent activity, its rapid availability and high intensity activity. The next question is: How much and how often?

DOSAGE OF INSULIN

The amount of insulin required must be individualized. It is the amount required to produce the therapeutic effect desired. This may vary from 100 to 5000 units in the first 24 hours. Insulin must be given with full appreciation of the urgent necessity of restoring carbohydrate metabolism as rapidly as possible without endangering the patient with severe hypoglycemia. This goal can be achieved by following certain "rules of thumb" and the use of educated guessing, or as the psychologists say, "the integration of the unconscious associative processes with past experience."

The three factors that help determine the initial insulin dosage are: the age of the patient, the severity of the acidosis, and its duration. As a rule, older people should receive less insulin initially than younger patients. An average starting dose of insulin for patients over 45 years of age who manifest intensive glycosuria and ketonuria is 50 units an hour. With the younger

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patients, it is more common to give from 75 to 100 units an hour for the initial dosage. However, since the amount of insulin administered is to some extent dependent upon the type of fluid administered, this subject will be reopened further along.

ACIDOSIS, DEHYDRATION, AND SALT DEPLETION

The hyperglycemia and resultant glycosuria initiate a chain of events that result in the clinical picture of acidosis. The diuresis provoked by the glycosuria drains tremendous amounts of salts from the body. The hyperglycemia increases the effective osmotic pressure of the blood and consequently draws water from the cells which in turn became dehydrated. This water drawn from the cells dilutes the extracellular components with resultant apparent decrease in concentration of the blood sodium and chloride. At the same time there is an increase in the concentration of the circulating potassium. Since we know that the diuresis causes a marked loss of potassium from the body, and the draining of the intracellular fluid to the extracellular spaces dilutes the circulating solutes, then the observed increase in potassium concentration is a manifestation of a tremendous discharge of potassium from the cells to the extracellular fluid. This release of potassium from the cells is probably related to the interference with carbohydrate metabolism. With the return of adequate carbohydrate metabolism under the influence of insulin, there is a decreasing concentration in the serum which will be discussed later.

In addition to the salt loss, the diuretic effect of the glycosuria produces dehydration. These changes are responsible for the circulatory disturbances which are the immediate threat to the patient's life. This discussion is not intended to minimize the acidosis per se which results from the ketosis. However, so much discussion in the past has been given to this aspect of the subject that it will be handled very briefly. In the intermediary metabolism of fat the 4 carbon chain acids are produced. Normally these are oxidized at a rate sufficient to prevent their accumulation. In the absence of adequate carbohydrate metabolism the rate of production of these 4 chain ketotic acids is increased. Since their rate of oxidation is not materially increased there is an accumulation in the circulating blood. Base is required to neutralize them and they are excreted as the sodium and ammonium salts to a large extent. This loss of base from the body results in the decreased alkaline reserve or acidosis. This brief discussion on the mechanism of the production of the dehydration syndrome is given as a background for the discussion of the choice of fluid to be used for intravenous therapy to combat this major immediate threat to the patient.

PARENTERAL FLUID THERAPY

The most widely discussed point in this respect is whether or not glucose should be administered intravenously in the treatment of diabetic coma.

The pros argue that hyperglycemia facilitates the combustion of glucose. The small increase in glucose combustion obtained this way can be obtained by increasing the insulin dosages. Insulin is still the most effective stimulation of glucose metabolism.

The cons argue that hyperglycemia provokes glycosuria with its attendant dehydration and the administration of glucose defeats its own purpose. Both schools of thought are correct. The solution to this perplexing therapeutic problem is not too difficult if one does not take an arbitrary extreme point of view.

Immediately after the initial dosage of insulin, it is my practice to give normal saline intravenously. This solution is continued until evidence is obtained that the administered insulin is exerting its action on the concentration of sugar in the blood and urine; the insulin being administered in hourly doses of 50 to 100 units. If, after four hours, there is no evidence of decreasing hyperglycemia and glycosuria or ketonemia and ketonuria then the hourly insulin dosage is increased. Those patients who will fall into the category of the insulin resistant can be detected within the first four hours and their lives saved by aggressive insulin administration above usual requirements, and further investigation for complications. If glucose is administered immediately, it masks the earliest insulin activity as well as provoking increased diuresis. Once the evidence of insulin activity is available, then glucose may be added to the intraveous solution. The actual time interval between the first injection of insulin and the doses of intravenous glucose may be from one to six hours. In the initial plan of treatment, the exogenous source of glucose is not needed as the glycemic levels are usually well above 400 mg. in each 100 c.c. The imperative action is first to replace salt and water.

LABORATORY TESTS

Many guides have been suggested to use in determining the initial amount of insulin administered. Blood sugar levels, when and if available, are good. However, the holiday and week-end routine of many hospitals precludes its use. On week days, at best, an hour or more is

required to obtain an analytical result. This delay is dangerous to the patient. The analysis of the urine for ketones and glycosuria is much simpler and quicker.

Many physicians use an indwelling catheter. They believe the information obtained saves more lives than the occasional resulting pyelitis destroys. It is better to have a live patient with pyelitis than a dead one with a sterile urinary tract. Others will not catheterize their patients but depend on clinical judgement, plus analysis of blood when available. That is a personal choice, but all sources of information available should be used. In unconscious patients, it is absolutely necessary to catheterize. Furthermore, it provides a measure of renal function by watching hour to hour urinary secretion.

The recent popularization of the standard Rothera test for bedside determinations of blood ketones has much in its favor, particularly in determining initial doses of insulin. The higher the concentration of blood ketones determined by a simple dilution test the greater the initial amounts of insulin required.

POTASSIUM THERAPY

Another controversial point in the treatment of diabetic coma is the use of intravenous potassium. As stated previously, in untreated diabetic coma there is usually an increase in the serum potassium. When the administered insulin reaches its peak activity there is usually a decrease in serum potassium occasionally resulting in symptoms of potassium deficiency. Certainly, for the first four to seven hours of treatment it is dangerous to give potassium intravenously. If the patient is able to take any fluids or food by mouth, the intravenous administration is definitely not indicated as all fruit juice, boullion and most foods contain adequate amounts of potassium. After that, if real evidence of potassium deficiency exists, as shown by the flame photometer or electrocardiograph, then it is permissible to give it. When potassium chloride is given intravenously 30 m. equiv. or about 2.2 gm. per litre of saline or glucose is safe. Another contraindication is impaired renal function.

Alkalis are seldom administered intravenously. There are occasional patients whose loss of alkali reserve has been so great that they will benefit from this form of replacement therapy.

NUTRITION DURING CONVALESCENCE

To speed the convalescence of these patients it must be borne in mind that they have been through a severe catabolic episode. They have suffered extensive destruction of body protein and loss of vitamins with resultant interference with the enzyme systems. The prescribed diet should be more than the previous maintenance diet in the precoma period. Provision must be made for the nutritional rehabilitation and restoration of the protein reserves. Extra protein, in the presence of adequate calories, with supplementary vitamins in adequate dosage must be prescribed for a period of several weeks.

VOLUME OF FLUID

The question of the total amount of fluid to be administered is one of clinical judgement based upon the presenting signs. In face of circulatory collapse transfusions of whole blood are indicated.

The total amount of saline and saline plus glucose may vary from 4 to 20 litres. Fluids must be given until the specific gravity of the urine is restored to normal levels and tissue hydration is obtained. These amounts of fluid presuppose good renal functions and adequate circulatory status.

CONCLUSION

Basic principles in the treatment of diabetic coma are the immediate emergency measures and the management during convalescence. In the emergency measures, regular insulin is the therapeutic agent of choice. It must be given in adequate amounts with the full appreciation of the urgent necessity of restoring carbohydrate metabolism as rapidly as possible. Fluids must be given intravenously in true ketotic acidotic coma as soon as insulin treatment is started. The initial solution is physiologic saline solution.

The crucial time in the treatment schedule of the true coma patient occurs at about the 4th to the 7th hour. If there is no decrease in hyperglycemia or glycosuria, insulin administration must be pushed more aggressively as one must suspect unusual insulin requirements. If glycosuria and hyperglycemia start to decrease, then glucose may be added to the intravenous solution. If the flame photometer is available, serum potassium determinations, at this point, should be done and potassium salts administered only if definite indications exist.

The physician is reminded that true ketotic acidotic coma is a catabolic episode and that the patient loses excessive quantities of protein nitrogen from the body; therefore, in the diet prescription following such episodes, adequate provision must be made for the replenishment of the nutrients lost, such as protein, riboflavin, and other vitamins.

Pathology of Diabetes Mellitus

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To the pathologist whose principal concern is morbid anatomy, diabetes mellitus is not a clear cut entity. The histologic changes which are specific for this disease are strikingly few, and in fact, the only one which so far appears to be associated solely with diabetes mellitus is intercapillary glomerulosclerosis. The pancreas, which is the organ most directly concerned, shows variable and non specific lesions, whereas in other organs and tissues histologic alterations are not outstanding and are most easily interpreted as due to the metabolic disturbances related to insulin deficiency.

THE PANCREAS

As mentioned above, no specific lesions are uniformly encountered in the islets of Langerhans. In fact, one does not invariably find histologic abnormalities. Of those which do occur, however, hyalinization of the islets is the most typical. Although this same change may occur in nondiabetics, it is much less extensive, and much less common. The nature of this substance, and its manner of development remain obscure. It is always found in association with the capillaries of the islet, and makes its appearance first in association with the vessel wall. The nature of this substance is unknown, and it does not bear any relation to the similar appearing hyaline material found in intercapillary glomerulosclerosis, in that there is no parallel in the incidence of the two lesions. One striking feature of islet hyalinization is its prevalence in diabetics over 40 years of age. Despite the fact that the hyaline is found more commonly in diabetes of long duration and in individuals over 40 years of age, Shields Warren[1] makes the statement that it is a cause of diabetes and not a result. In my opinion this is a debatable statement.

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A second lesion, found in about one quarter of diabetics, is fibrosis of islets. This again is found in older diabetics and is often associated with hyaline. In its earliest stages it appears to begin as reduplication of the capillary wall. This has been described by Hartroft.[2]

Most of the textbooks describe hydropic degeneration of islet cells as a common finding. This lesion has recently stimulated great interest as Toreson[3] showed that the vacuolation represented in fact glycogen infiltration. This work has not been repeated by others, and awaits confirmation. The significance of glycogen infiltration of the islets is difficult to evaluate. Experimentally it can be shown to be an exhaustion phenomenon related to hyperglycemia. Furthermore it is reversible in its early stages at least.

At the beginning it was stated that diabetics with histologically unaltered islets are occasionally encountered. It is our experience that differential stains in these cases sometimes reveal a deficiency of beta cells.[4]

CHANGES ASSOCIATED WITH ABNORMAL CARBOHYDRATE METABOLISM

It is not surprising, in view of the profound disturbance in carbohydrate metabolism, that glycogen infiltrations are found in many tissues. Most commonly these are seen in liver and kidney. In the liver, it occurs in either nucleus or cytoplasm in the form of droplets. Strangely enough, it is not found in both sites at the same time. The large glassy appearing nucleus, greatly distended, is an expected finding at autopsy in the diabetic, but it also occurs in other unrelated conditions. In the kidney vacuolation due to glycogen droplets is seen in Henle's loop and in convoluted tubules. In other locations similar infiltrations are found, for example in myocardial muscle fibres, in the stratum corneum, and epithelium of hair follicles, and sweat glands in skin, and in the pigmented epithelium of the iris.

These depositions are reversible and are significant in the skin, which is thereby rendered much more suscepti-

ble to infection, and possibly in the pancreas, where such infiltration may be an indication of cellular injury.

CHANGES ASSOCIATED WITH ABNORMAL FAT METABOLISM

The single most important result of abnormality of fat metabolism in diabetes is the development of atherosclerosis at an earlier age, and to a greater extent, than in nondiabetics. Other results of disturbed fat metabolism are found in spleen, where lipid filled reticulum cells are seen; in skin, where xanthomata may develop; in gall bladder, where the incidence of stones and cholecystitis is increased; sometimes in liver, which may show fatty metamorphosis; and in the kidney showing intercapillary glomerulosclerosis. These latter changes are most probably directly related to hyperlipemia.

In considering atherosclerosis, diabetics do not show any differences of distribution from nondiabetics, although the involvement of small muscular arteries of lower extremities may be more marked. The lesions in the intima are identical in both groups of cases. Not only is the diabetic predisposed to atherosclerosis, but also to the development of medial calcification, or Monckeberg's sclerosis. These two lesions are not necessarily associated with one another. The reason for the diabetic's enhanced susceptibility to arteriosclerosis remains obscure. Theories as to the etiology of atherosclerosis have been numerous over the years, and the fashion changes frequently. First regarded as a process natural to aging, later investigators turned to injury to the vessel wall as a predisposing factor. In more recent years, as more has been learned of fat metabolism, and the frequent association of hyperlipemia with the development of atherosclerosis noted in diabetes, myxedema and other entities, an extensive investigation of blood lipids has been undertaken by many investigators.[5, 5-a] As Warren[1] has stated, these investigations have been directed towards answering two questions: a) Is the level of serum cholesterol related to the degree of atherosclerosis in a given individual, and b) Is the level of serum cholesterol related to the dietary intake of this substance?

Conflicting evidence has been produced in answer to both questions. There is some support for the belief that hypercholesteremia is related to atherosclerosis, but little relationship between dietary cholesterol and blood cholesterol levels can be established. The work of Gofman[6] and his associates, in revealing an abnormal lipid pattern in atherosclerosis, gives considerable support to those who believe in the importance of blood lipid level, in that there appears to be an association of abnormally large lipoprotein molecules in plasma with the development of atherosclerosis. For the past few years, however, despite the most detailed clinical and experimental investigations, it has become increasingly apparent that abnormal blood lipid patterns are not the sole cause, nor even possibly the principal cause of atheroma. Recently a different approach to the problem has been made, and this goes back to first principles.

For many years, and in fact still, there has been much dispute concerning the pathogenesis of atheroma. Is the fat, which is in the intima of the blood vessel wall, located, in the earliest stages, in cells, or in intercellular substance? Is the fat carried into the wall by lipophages, or does it reach the intima by imbibition? Part of the solution to these problems has been given by Duff and McMillan,[7] who have shown that in the rabbit the earliest detectable change in the vessel wall is an alteration in intercellular ground substance, followed by the development of fat droplets in the intercellular material. The subsequent development of the atheroma obscures this, in that fat accumulates in lipophages, and in intercellular substance, with surrounding fibrous tissue proliferation and later necrosis, calcification and ulceration. The importance of these observations lies in the emphasis placed on the alteration in intercellular ground substance as a change preceding the appearance of fat.

If we now consider those entities characterized by marked atherosclerosis we find a possible connecting link in the altered ground substance, or intercellular material. This consists of complex mucopolysaccharides, whose integrity is dependent upon a variety of hormones, such as cortisone, thyroxin, and estrogens, and upon vitamin C.[8] We find, too, that in older individuals, this ground substance in some situations, such as the wall of the aorta, increases in amount and shows some histologic alteration in character. Here, then, is the most recent, and certainly the most promising hypothesis regarding the etiology of atheroma, that the fundamental disturbance leading to accumulation of fat and lipoid in the vessel wall is an alteration in intercellular ground substance. This is hypothesis only, at present. When one attempts to extend this theory to the atherosclerosis of diabetes mellitus, there is some relation, in that the mucopolysaccharides of intercellular substance must conceivably be affected by the profound disturbance in carbohydrate metabolism. In fact, Shields Warren[1] and others[9] have described alterations in intercellular ground substance in the skin of diabetics.

In summary, one may say that although elevation of blood lipids and possibly alteration in blood lipid pattern play an important role in the etiology of atherosclerosis, of equal if not greater significance may be alterations in the vessel wall, and especially in the intercellular ground substance. In reaching this conclusion we have gone a full circle, and are back to Virchow's original hypothesis, as enlarged and modified by Aschoff,[10] that local loosening of intercellular cement substance, due to mechanical stress, is followed by imbibition of lipid-containing fluid from the blood plasma into the vessel wall.

THE KIDNEY

As part of the complicating arteriosclerosis, renal changes, such as benign nephrosclerosis, are common. Less commonly pyelonephritis develops, and acute necrotizing papillitis, a complication of pyelonephritis with an obscure pathogenesis. Of great interest, but of debatable incidence, is the intercapillary glomerulosclerosis first described by Kimmelstiel and Wilson.[11] In this complication there is the deposition of hyaline-like material, in nodular pattern, in the central part of the glomerular lobule. Usually an intact capillary is seen at the periphery of the hyaline mass. Frequently the efferent arteriole as well as the afferent, show similar hyaline thickening of their walls. This lesion is apparently specific for diabetes mellitus, and has not been described in any other condition. Tubules may show varying degrees of degenerative change secondary to obstruction of blood flow through the glomerulus, as often the whole glomerular tuft becomes converted into a functionless hyaline mass. The nature of this lesion is obscure, as pathologists disagree about its pathogenesis. Whether the hyaline material has its origin in the capillary wall, in the connective tissue of the glomerular stalk, or is deposited in the intercapillary space remains unsettled. In view of the theory advanced earlier, that there is a disturbance in mucopolysaccharide metabolism, one is inclined to favor the glomerular lesion as originating in the capillary wall, the basement membrane of which is composed of mucopolysaccharides. Support for this belief is found in the capillary lesions of the retina.

A second form of hyalinization of glomerulus is seen in diabetics. This has a diffuse distribution, but is non specific and is seen in essential hypertension, and in chronic glomerulonephritis of both the human and experimental types.

THE EYE

The last group of lesions to be mentioned are those occurring in the eye. It is difficult to dissociate retinal changes in diabetics from associated hypertension, and renal disease. It is apparent, however, that there is a retinopathy seen only in diabetics. This is due chiefly to the development of microaneurysms of capillaries. The incidence of these lesions parallels closely that of intercapillary glomerulosclerosis. One finds small spherical outpouchings of the capillary wall, often with dilated retinal veins, and small hard white exudates composed of protein. These have been well described by Friedenwald.[12] The capillary aneurysms are of great interest, because these lesions lend support to the theory of disturbed mucopolysaccharide metabolism resulting in weakening of capillary wall, with aneurysm formation.

Other eye changes, such as retinitis proliferans, are the result of organization of hemorrhages.

Lens opacities are commonly associated with diabetes mellitus, even in the younger age group, but statistical evidence that the incidence of such opacities is higher in diabetics is conflicting.

SUMMARY

In diabetes mellitus the commonest lesion in the pancreas is hyalinization of islets of Langerhans. Fibrosis, and glycogen infiltration are found less commonly. Occasionally no histologic alteration can be seen.

Glycogen infiltrations in liver and kidney are not significant, but in the epithelium of hair follicles, and sweat glands of skin enhance the susceptibility to infection.

Disturbance in lipid metabolism results in premature development of atherosclerosis, in cholelithiasis and cholecystitis and possibly in intercapillary glomerulosclerosis of kidney.

The importance of disturbance of mucopolysaccharide metabolism is discussed as a predisposing factor in the development of the atherosclerosis, the intercapillary glomerulosclerosis, and microaneurysms of the retina.

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The Undernutrition Treatment of Diabetes

Just at my entrance into the war in 1918 I wrote the following sentences in a paper planned for delivery before the Johns Hopkins Medical Society and presented for me by Dr. Sidney Miller. "At the beginning of 1914, the outlook for diabetic patients was depressing. The statistics of the Massachusetts General Hospital showed that in the preceding 16 years for each 100 diabetics submitted 28 were discharged dead, a record which duplicated the experience of the hospital between 1824 and 1898. Physicians dreaded to place their patients in an institution lest the treatment there prescribed prove more disastrous than that adopted by the patient's fancy. Surgeons dodged the diabetic, while the obstetrician was out and out afraid of diabetes and urged pregnant women to have abortions. The neurologist, dermatologist would throw up their hands at complications within their respective spheres and exclaim, 'Cure the diabetes and then we will help the patient.' It is hard to realize that these conditions prevailed over four brief years ago.

"As so often happens when the clouds are darkest, light unexpectedly appears, and I recognized its approach one afternoon while talking with Dr. Allen. It happened in this way: We were discussing one of my several cases (Case No. 344) and I pointed out how the type of diabetes in this instance changed from severe to mild as tuberculosis came on and the patient progressively became weaker and lost weight. I remember telling Doctor Allen that if he could explain why this change took place the problem of diabetic treatment would be greatly advanced. The next day I heard from him that he felt he could explain the reason for the improvement, and furthermore believed that he would be able to demonstrate the cause for it by experiments on animals, and soon after I was gratified to learn how doctors could give their diabetic patients renewed hope. You are familiar with his experiments by which he showed that dogs made artificially diabetic and then forced to lose weight gained in tolerance for carbohydrate.

"This striking improvement in diabetic treatment belongs to the first year of the disease, the year which I call the diabetic's danger zone. This is important, for it is the most useful year to the diabetic and to the community. The first year of the disease is preeminently the year of coma. Eighty-seven per cent of all diabetics who have come under my care and have later died during the first year of the disease have succumbed to it. And yet today everyone will agree that diabetic coma during the first year of the disease should be considered an accident which can and should be avoided not only in adults but in the youngest child."

From *Diabetes Yesterday, Today, and Tomorrow,* by Elliott P. Joslin, M.D., in *Proceedings* of the American Diabetes Association 1:124-125, 1941.

DIABETES IN ICELAND

Valtyr Albertsson, M. D. REYKJAVIK, ICELAND

Until recent times few clinical observations on diabetes were available. A thesis on diseases in Iceland, written by Finsen[1] and based on his experience as a doctor in the northern part of the country in the decade 1856-1866, contained his conclusion that diabetes must be regarded as a very rare disease as he himself had not seen a single case. He was a well-educated physician, a keen observer and had practiced for a period in Denmark. At the turn of the century Bjornsson,[2] one of the most experienced doctors in Iceland, also expressed the opinion that diabetes was a rare disease among Icelanders. In 1938 Jónsson,[3] the director of Public Health also stated: "Diabetes is a very rare disease in Iceland, and it is an extraordinary occurrence for doctors to come across it."

Several doctors and institutions are still of the opinion that diabetes is a rarity in Iceland. A gastroenterologist informed me that one diabetic was found during the last ten years among 3,300 gastroenterological cases. He confessed that care was not always taken to collect the urine after meals so that incipient cases might have escaped detection. A life insurance doctor also thought that diabetes was very uncommon. Among 2,087 admissions in two tuberculosis sanatoria, diabetes was not found in a single case.

In my mind there is, however, no doubt that diabetes is more common now than 22 years ago when I first was on the lookout for it. According to my calculations, there were about 30 known diabetics in Iceland in 1930. In January, 1942, I sent a questionnaire to all active physicians in Iceland and asked them to give me the name, age, occupation, state of health and all possible information about the diabetics they had under treatment or knew to have the disease. Practically all answered; 63 diabetics were reported (one in 2000 of the population). In 1947, 94 cases were reported to me, and now I estimate that there are about 140 known diabetics in Iceland or a little less than one per thousand.

In my practice, I have routinely tested the urine for sugar and if positive, I have always made a blood sugar test. Among my first 2,000 patients, some 20 years ago, one diabetic was found. During the last three years, I have examined more closely 1,613 Icelanders, of whom 76 per cent were over 40 years of age. Urine was collected and a blood sample taken about 60 to 90 minutes after a full meal. If glycosuria was found and/or blood sugar above a screening level which was chosen at 130 mg. per 100 cc., a modified glucose tolerance test was done. The number of diabetics discovered was seven.

During the fall of 1950 I examined 1479 individuals (about 59 per cent) of the 2,500 inhabitants of Akranes, a town near Reykjavík. Blood and urine tests were made for persons of thirty years and over. Younger patients had only a test of urine, and in these cases absence of glycosuria was assumed to mean freedom from diabetes.

A retired physician of 81, who had practiced there for 42 years, told me that he had never found diabetes in Akranes. The inhabitants numbered only 755 in 1901 and about 1700 when he retired. I learned, however, that a little girl from Akranes had died from diabetes in 1933, and that a sixty year old obese man was found to have mild diabetes in 1949 while being prepared for cholecystectomy. He was found to be without glycosuria when he was on a restricted diet, but a glucose tolerance test showed that he was not cured.

My studies disclosed three additional cases. One of these patients had definite symptoms, but two others were without complaints. None of them had consulted the local physicians during the preceding twelve months. There were also three cases in which I advised supervision; quite recently I found one of these individuals to have incipient diabetes.

Address communications to Doctor Albertsson, Tungata 3, Reykjarik, Iceland.

My rather incomplete survey seems to have made the town more diabetes conscious. A 15 year old boy, a near relative of one of the diabetics I found, who had been out of town during my stay at Akranes, was soon afterwards sent to me with vague complaints. I found that he had mild or incipient diabetes. In February 1952, the sixth case was discovered by means of a glucose tolerance test. Consequently, there are now seven known diabetics in Akranes. This represents an incidence of 2.6 per thousand since the population is now 2,700.

I wonder if there are relatively more unknown cases in Iceland than in other countries.

LIFE EXPECTANCY IN ICELAND

My countrymen live long enough to give diabetes opportunity to become manifest. The life expectancy for males at birth rose from 48.3 years at the beginning of this century to 60.9 years in the decade between 1931 and 1940. For females the corresponding increase was from 53.1 to 65.6 years. The Statistical Bureau has informed me that it has increased further.

TABLE 1.

LIFE EXPECTANCY AT BIRTH IN ICELAND

	Males	Females
1902-10	48.3 years	53.1 years
1911-20	52.7 years	58.0 years
1921-30	56.2 years	61.0 years
1931-40	60.9 years	65.6 years

MORTALITY STATISTICS

Detailed mortality statistics became available in Iceland in 1911. These statistics seemed to corroborate the view derived from clinical observations regarding the rarity of diabetes.

From 1911 to 1930 the annual death rate from diabetes in Iceland was 1.8 per 100,000 inhabitants. In a few cases diabetes was mentioned as the contributory cause of death, some other diseases being accorded the priority. Yet even if they are included, the mortality figure reaches only 2.1 per 100,000. The number of males and females was equal.[4]

I found after 1930 that the Statistical Bureau did not classify diabetes as a cause of death according to the rules of joint cause classification of causes of death[5-7]; the primary cause of death was usually recorded according to the judgment of the certifying physician. In studying the death certificates for the years 1931-1950, I found that in some instances where diabetes was mentioned, priority was accorded to other conditions such as chronic nephritis, arteriosclerosis, heart disease and senile marasmus. I therefore reclassified diabetes as a cause of death. The annual death rate was then 1.9 to 4.0 per 100,000.

During this period, 1931-1950, females outnumbered the males in the mortality statistics; they constituted 58 per cent of the total number.

TABLE 2.

DIABETES MORTALITY IN ICELAND

	Annual Death Rate Per 100,000 Living Inhabitants	
	All Iceland	City of Reykjavik
1931-35	2.8	4.5
1936-40	1.9	2.2
1941-45	1.9	3.3
1946-50	4.0	6.2

The deaths from diabetes in the city of Reykjavik are higher—2.2 to 6.2 per 100,000, than for the country as a whole. Here, diagnostic facilities have been good; since 1938 glucose tolerance tests have been performed free of charge. The higher recorded mortality in Reykjavik is certainly due in part to closer medical supervision, but this is not the sole cause. I know some patients who moved to Reykjavik only because they had diabetes.

FACTORS INFLUENCING THE INCIDENCE OF DIABETES

According to Joslin[6], the statistical incidence of diabetes is highest where the urine tests are most frequently performed, where the inhabitants live longest, and where they weigh the most.

In Iceland, as in other countries, physicians differ. Some are wise and careful and practically always test the urine; some are different in this respect. Iceland is a sparsely populated country and formerly the physicians were few and far between. In 1915 there was one doctor per 1,300 inhabitants. In recent years, the ratio has risen to 1 per 800 or 900. In 1910 only 32.2 per cent of the people lived in towns and villages; in 1950 this percentage had risen to 72.3. Most people now live within easy reach of a physician and better means of communication have made medical supervision easier in the rural areas too. The mortality rate is becoming very low (7.9 per thousand in 1949 and 1950); life expectancy is steadily increasing.

INCIDENCE OF OBESITY

As a boy, 40 years ago, I rarely saw obese people, but overweight is now quite common. The machine age with lessened demand for physical labor and the shorter working day has also come to Iceland although at a somewhat belated date. Steffensen[8] has found that height of the people has increased considerably during recent decades. He attributes this to less physical labor during adolescence; to improved diet, in some respects at least; and to better conditions of living generally. Whatever may be the reason, the population is growing taller; there is also an increasing tendency to overweight, especially in the middle-aged.

DIET IN ICELAND

For centuries the diet has been unusually rich in protein and fat (derived from milk, meat and fish), but low in carbohydrate.

TABLE 3 THE COMPOSITION OF THE DIET IN ICELAND

	Per Cent	18th Century	1850	1940 Country	1940 Towns
Carbohydrate	"	24	30	40.3	44.2
Protein	"	33	28	19.2	17.9
Fat	"	43	42	40.5	37.9
Animal Food	"	90-95	80-85	57.9	45.6

The figures for 1940 were based on the dietary survey made in 1939-1940.[9] The caloric intake was then found to be 3,090 for adult males in towns and 3,553 in the rural areas. The increase in respect to carbohydrate is derived mostly from white bread, potatoes, and refined sugar. The consumption of sugar has risen greatly. The figures for the 18th century and 1850 are Steffensen's estimates,[8] based on statistical data and various other kinds of information.

RELATION OF FAT AND PROTEIN TO THE INCREASE OF DIABETES

Himsworth[10] made an interesting study on the frequency of diabetes in relation to the quantitative composition of the diet in different countries. He concluded that a diet relatively high in fat predisposes to diabetes. Young[11] found that a diet high in protein, especially meat, given experimental animals increases susceptibility to the diabetogenic action of anterior pituitary extract to a greater extent than does a high carbohydrate diet. He also mentioned the possibility that a diminution in the consumption of animal protein during wartime might be a factor of significance in the fall of diabetic mortality associated with food rationing.

In spite of these observations, the conditions in Iceland seem to show that a diet high in animal protein and fat is not accompanied by a high incidence of diabetes in the population.

SUMMARY

Diabetes, which was considered a rare disease in Iceland up to fairly recent times, is now diagnosed with increasing frequency. It is estimated that there were 30 cases, or about 1 in every 3,500 inhabitants in 1930, as compared with 140 cases, or 1 per 1,000 population at present. The death rate from diabetes in Iceland has increased from 1.8 per 100,000 population in 1911-1930, to 4.0 in 1946-1950. In the capital city of Reykjavik, the death rate has been consistently higher than in the whole country in each 5-year period from 1931-1935 to 1946-1950. Females account for approximately 60 per cent of all deaths from the disease.

The increase in known frequency of diabetes in Iceland reflects the increased length of life of the population, changed dietary habits, easier working conditions, and, last but not least, a closer medical supervision.

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Diabetes in Two Ontario Communities

Studies in Case Finding

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In an earlier report the authors[1] gave the results of a diabetes survey in the town of Newmarket, Ontario. In the present paper the results of similar surveys in two widely separated towns are presented.

In the Newmarket survey[1] 4419 persons were examined for diabetes, both blood and urine samples being tested for sugar. Eighty-one per cent of the town's population over the age of six were covered by the survey. Fifty-six diabetics were seen—an incidence of 1.27 per cent of the tested population. Twenty-three of this number, or 0.52 percent, were previously undiagnosed. These results are in general agreement with those from other case finding surveys which have all shown the need for upward revision of earlier estimates of the prevalence of diabetes based on vital statistics.

The group tested in Newmarket was predominantly of British origin. In planning further surveys, two towns were chosen so as to include fairly large groups with a different racial origin. The towns selected were South Porcupine, a gold mining town in Northern Ontario with a mixed population, and Hawkesbury, a town in Eastern Ontario close to the Quebec border and containing a large proportion of French-Canadians. The main source of employment in this second town was concerned with the production of wood pulp.

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This research was carried out under the Ontario Provincial Department of Health with funds made avaliable through the National Health Grants of the Dominion Government.

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METHOD

The procedures followed in these surveys were identical with those already described in the Newmarket[1] survey. The methods are summarized below and reference should be made to the previous paper for a more detailed account. Postprandial capillary blood and urine samples were examined from each person seen at the testing clinic. Urine samples were tested qualitatively with Clinitest.[2] Positive results were usually confirmed by a quantitative estimation on the same urine sample, using Benedict's quantitative reagent. Capillary blood samples, taken from the earlobe or finger tip, were estimated by a modified Somogyi Nelson technique; [3-5] protein precipitation was effected by the method of Herbert and Bourne,[6] in which the isotonicity of the solutions used prevents hemolysis. This technic gives true glucose values for blood.

All age groups, with the practical exception of the preschool group (under six years) were tested. Various schemes were used to obtain as wide a coverage as possible. Portable equipment enabled the testing clinic to be set up wherever necessary—in schools, factories and in other public buildings in different areas of the towns. Publicity was secured through the newspapers, posters, circular letters and by house-to-house canvassing undertaken by volunteers from many service clubs and other organizations.

TABLE 1 A summary of the criteria for blood sugar values used in screening and diagnosis

Test	Blood Sugar mg. per 100 cc.	Time after meal	Interpretation
Initial Test	>160 >150 >120	up to 1½ hrs. 1½-2 hours 2 hours or fasting	abnormal—recheck made
Initial Test + Recheck Test	both >200	anytime	diagnostic of Diabetes
Glucose Tolerance Test (50 gm. Glucose 2 hour curve)	>120 >200 >120	 fasting at peak 2 hours	diagnostic of Diabetes together diagnostic of Diabetes

TABLE 2 Population of the towns surveyed (information taken from Town Assessment Records) and the proportion in each group covered by the survey

	SOUTH PORCUPINE			HAWKESBURY		
Age Groups (years)	Population from town census	Population Tested	Percent Tested	Population from town census	Population Tested	Percent Tested
all ages	5058	3163	62	7017	3510	50
0-5 yrs.	696	115	17	1193	14	1.2
6 yrs. and over	4362	3048	70	5824	3496	60.5
6-19 yrs.	1294	1192	92	2053	1611	78
20-59 yrs.	2799	1688	60	3217	1640	51
60 and over	269	168	62	554	244	44

The criteria used in interpreting blood sugars, both for screening purposes and for diagnosis are shown in Table I. Persons showing abnormal blood sugar levels (i.e.—in excess of screening values), or glycosuria were re-examined. Diabetes was diagnosed only when the blood sugar, after food, was elevated above 200 mg. per 100 cc. on two or more examinations. When such results were inconclusive, a glucose tolerance test using capillary blood samples was performed following 50 gm. glucose taken orally. Diabetes was diagnosed if both the peak and the two-hour level were abnormal—above 200 and 120 mg. per 100 cc., respectively. New diabetics were referred to their own physicians for treatment.

RESULTS

Population Surveyed In South Porcupine, 3163 persons from a population of 5058 were examined. Excluding those under six years in the population, 70 per cent of the remainder were tested. In Hawkesbury, 3510 persons were tested in a population of 7017—a coverage of 60.5 per cent of those over six years. Table 2 shows in more detail what proportion of each of several age groups were examined in the two surveys. The survey was more successful in testing the school children than in reaching the adult population.

In presenting all further analyses of the results of the two surveys, the data from each have been aggregated. The total sample tested was, therefore, 6673 persons.

The age and sex distribution of the tested population is set out in Table 3 with similar values representing the population of Ontario for comparison. It will be seen that the main differences are: 1.) A deficiency in the preschool age groups in the tested population compared with that of Ontario. 2.) An excess of the school age groups. 3.) A slight excess of females from 30 to 49 years. 4.) A deficiency in numbers, becoming more marked with increasing age, in the remaining adult age groups.

The racial origin of the tested population is shown in Table 4. Nearly half were of French origin and about a third were of British descent. About 7 per cent were Scandinavian, the remaining 10 per cent were made up of small numbers of other groups, as shown.

Diabetics A total of 87 diabetics were seen, among 6,673 persons tested, an incidence of 1.3 per cent. Thirty-five of these diabetics were new cases; i.e. were previously undiagnosed and were not under medical supervision for diabetes. These new diabetics constituted two-fifths of the total and represented an incidence of 0.52 per cent of the tested population. The remaining 52 cases were previously known diabetics already under treatment. They represented 0.75 per cent of the tested population.

Figure I shows the age and sex distribution of the 87 diabetics. Females outnumbered males in the ratio of 56 to 31, and predominated in each age group through sixty-nine years. Most of the diabetics—nearly two thirds of the total—fell within the twenty year period from age 50 to age 69. There were no juvenile diabetics in the group.

Forty three of the cases (about 50 per cent of the total) occurred among those of French origin. Of the remainder, 26 per cent were British, 9 per cent Scandinavian, 8 per cent Slavic, 5 per cent Italian and 1 per cent each middle European and Asiatic. If these figures are compared with those in Table 4, showing the origin of the tested population, it will be seen that the figures are, in the main, similar. The Slavic group—Poles and Ukrainians—show the greatest divergence,

TABLE 3 Age and Sex Distribution of Ontario Population Tested Population and Diabetics

Age In Years	Percentage of Population In Each Group				Number of Persons In Each Group		Number of Diabetics In Each Group					
	Ontario*		Tested Population In South Porcupine and Hawkesbury		Tested Population In South Porcupine and Hawkesbury		New Cases		Known Cases		Total Cases	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
0-9	9.4	9.0	8.8	9.2	580	615						
10-19	7.4	7.22	12.0	13.9	800	937						
20-29	8.22	8.10	5.5	7.2	366	479	—	—	—	1	—	1
30-39	7.50	7.35	6.3	8.2	423	549	—	3	2	2	2	5
40-49	6.40	6.10	6.4	7.3	433	488	1	9	4	2	5	11
50-59	5.30	5.10	4.3	4.6	280	310	2	8	7	13	9	21
60-69	3.80	3.75	2.5	2.4	162	156	5	5	5	11	10	16
70-79	1.95	2.00	0.6	0.65	41	42	1	—	3	2	4	2
80-	0.62	0.79	0.1	0.05	7	3	1	—	—	—	1	—
Total	50.59	49.41	46.5	53.5	3093	3580	10	25	21	31	31	56

*Estimated Population for Ontario, 1949, taken from Vital Statistics—Analytical Report No. 1 (Dominion Bureau of Statistics, Ottawa, 1948).

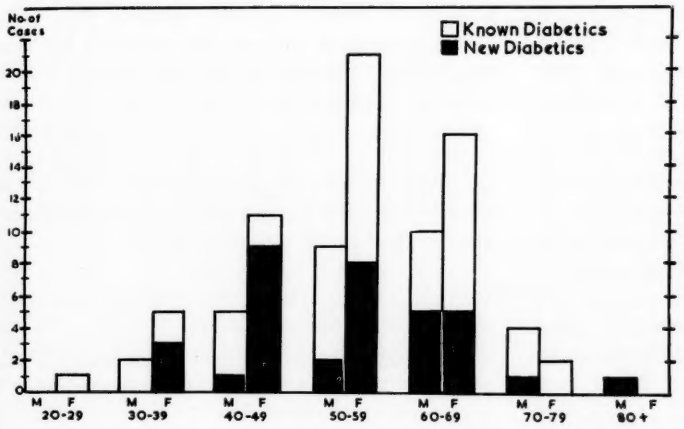

FIGURE 1 Age and Sex Distribution of 87 diabetics, both known and new cases, in South Porcupine and Hawkesbury, Ontario.

TABLE 4 Racial Origin of Persons Tested

Origin	Number Tested	Percent Of Total
French	3,225	48.5
British	2,120	31.8
Mixed, French and British	206	3.1
Scandinavian (mostly Finnish)	445	6.7
Middle European (mixed group including Germans, Yugoslavs, Rumanians)	226	3.4
Italian	218	3.3
Slavic (Ukrainian, Polish)	223	3.3
Asiatic	10	0.1

with 3.3 per cent of the population contributing 8 per cent of the diabetics. However, apart from the two main groups—French and British—the numbers tested are small and do not permit any valid deductions on this question.

Known Diabetics There were 52 known diabetics in the group. Many other known diabetics were also seen but are not included in this total as they were resident outside the areas covered by the survey. The incidence of known diabetics in each of the two towns was about 0.7 per cent of the number tested. It is difficult to know whether this figure underestimates or exaggerates the true incidence in the towns as a whole. An attempt was made to compile a separate list of known diabetics from physicians' records, but, for various reasons, a complete list was not practicable. Certainly there were some names, so obtained, of diabetics who did not attend the clinic, but it is not possible to say whether the proportion of diabetics who stayed away from the clinic was greater or less than the proportion of nondiabetics who did so. If it be argued that all the possible diabetics attended

the clinic, then the 52 known cases seen would represent an incidence of about 0.5 per cent of the towns' population over six years of age.

In most persons in this group, the onset of diabetes was after the age of 40. In only one was the onset during childhood, and in only eight was it below the age of 40. The average duration of the disease was six years. About half the number were taking insulin, the average dose being 29 units. It is difficult to comment on the status of the diabetic control of these patients on the basis only of one isolated examination, particularly when this was usually made soon after a meal. Half the group had sugar-free urines, and over half had blood sugars below 200 mg. per 100 cc. On the other hand, 11 persons, or about a fifth, had glycosuria graded 3 or 4 plus and twelve had blood sugar values in excess of 250 mg. per 100 cc.

New Diabetics There were 35 previously undiagnosed cases in the group, or 0.52 per cent of those tested. In Figure I, the black areas in each column represent these cases. Twenty five were female and ten were male. In each of the three 10-year age groups from 40 to 69, ten new diabetics were discovered. Among the 11 women aged 40 to 49 who were diabetic, no less than nine of them were previously unaware of the disease.

Twenty three of the 35 new cases were diagnosed on the results of postprandial blood and urine examinations. Twelve were diagnosed with the additional aid of glucose tolerance tests. Table 5 summarizes the blood sugar levels in both these groups. While all these cases showed initial blood sugar levels in excess of the screening levels, there were seven who failed to show any glycosuria in the initial sample. Urine samples obtained at later examinations were positive in these cases. But had the survey relied solely on urine examination for screening, seven diabetics would have escaped recognition —20 per cent would have been missed.

Five months after the completion of the survey in South Porcupine a second visit was made and 16 of the 17 diabetics discovered previously were re-examined. Unfortunately it was not possible to make a similar follow-up in Hawkesbury, so that the records were not completed on the 18 cases discovered there. In general, the follow-up results showed an improvement over the initial tests. Two persons had achieved normal postprandial blood sugar levels without insulin. Both of these were very obese women who had levels of 260 mg. per 100 cc. and above at diagnosis. Six months later when they had lost 20 to 30 pounds in weight, the blood sugar was normal, and the urine was sugar free after food. Two other patients showed higher blood sugar levels, after meals, than previously; while four others showed a decrease in the blood sugar, but not to normoglycemic levels. A glucose tolerance test was repeated in the seven cases who had previously been tested in this way. While none of these had reverted to normal tolerance, six had shown an improvement in tolerance of varying degree. In contrast, one patient showed a marked impairment in her tolerance. She had gained slightly in weight, whereas all but one of the others had lost. Only two patients in the whole group were taking insulin at the time of the follow-up.

Doubtful Cases There were eight persons whose results, while not indicating definite diabetes, were nevertheless suspicious. They fall into two groups. First, there were four persons who received glucose tolerance tests in the survey at South Porcupine. The original tests showed borderline diabetic curves. The tests were repeated during the follow-up study about six months later, and were completely normal. This change in glucose tolerance was achieved without any serious dietary restriction, though it must be admitted that all four had lost weight in the interval between the tests. It is difficult to say whether the improvement represents a cure of diabetes brought about concurrently with weight reduction, or whether the original borderline curves were due to a temporary impairment of glucose tolerance. The remaining four persons in this group had results which fell just short of the criteria set for diagnosis, but must still be regarded as probable or possible diabetics.

If these eight cases are included in the total of new diabetics, making 43 in all, the incidence in the tested population would be raised from 0.52 to 0.65 per cent.

TABLE 5 Summary of the blood sugar levels in 35 new diabetics at the time of diagnosis.

12 Cases Diagnosed by Glucose Tolerance Test			23 Cases Diagnosed by Post-prandial blood sugars	
Blood Sugar Level mg per 100 cc.		No. of Cases	Blood Sugar Level mg per 100 cc.	No. of Cases
Fasting	< 120	4		
	120-149	4	200-249	5
	> 150	4		
			250-299	8
Peak	200-249	6		
	250-299	4	300-349	8
	> 300	2		
			350-399	1
2 Hour	120-149	0		
	150-199	7	> 400	1
	> 200	5		

Glycosuria Table 6 summarises 188 cases in which glycosuria was found on the first examination at the clinic. In compiling this table, 92 of the total were taken from the Newmarket Survey.[1] These have been added to a further 96 cases from the South Porcupine and Hawkesbury surveys in which glycosuria appeared in the initial specimen tested. The total population examined in all three surveys amounts to 11,092 persons. The incidence of glycosuria as revealed by the qualitative test used is, therefore, 1.7 per cent. Excluding the known diabetics from the total, there were 146 unexplained cases of glycosuria, of which 100 were proven to be of nondiabetic origin, and 46 (or 31 per cent) were due to previously undiagnosed diabetes. When only a trace of sugar was present the diagnosis of diabetes was established in only 9 per cent, but when the glycosuria was graded 3 plus or 4 plus, diabetes was established in 70 per cent of the cases.

TABLE 6 Analysis of 188 cases showing glycosuria in the initial urine test. 92 cases from the Newmarket survey have been included with 96 cases found in South Porcupine and Hawkesbury.

Result with Clinitest	Total No. Positive	Known Diabetics	Total No. Excluding Known Diabetics	New Diabetics		Non-Diabetics	
				No.	%	No.	%
Trace	69	5	64	6	9	58	91
+ or ++	46	14	32	5	16	27	84
+++ or ++++	73	23	50	35	70	15	30
Totals	188	42	146	46	31	100	69

The Prevalence of Diabetes in Each Age Group As in the previous section, the results obtained in the Newmarket survey[1] have been used to increase the size of the sample. The total population tested is 11,092 and the total number of diabetics 143. Of this number, 58 were new cases and 85 were known diabetics, Figure 2 shows two pairs of curves, the first pair showing the total incidence of diabetes in each age group, the second pair the incidence of only previously undiagnosed diabetes. Of course, the numbers involved in constructing the graphs are relatively small, and it is unwise to generalize from these results. They are shown here because they illustrate the relative incidence of diabetes in the adult age groups tested in this series of surveys. It is surprising to see that, of the women from 50 to 69 years, 6.4 per cent, or one in every sixteen persons tested, had diabetes. In males this incidence of diabetes was not approached until the seventh decade (60 to 69 years) when 6.6 per cent were found to be diabetic. In revealing *new* cases, the greatest success was in testing those from 60 to 69 years. In males there were 3.3 per cent and in females 2.7 per cent new diabetics. In the two age groups from 40 to 59 years, relatively few men had undiscovered diabetes—0.25 per cent—whereas 1.9 per cent of the women tested were new diabetics. These figures serve to focus attention on the section of the public which harbours most of the diabetics. Moreover, in this section, diabetes may remain undiscovered for long periods and complications develop and progress before diagnosis. This is in contrast to the younger groups in whom diabetes has a more dramatic onset and

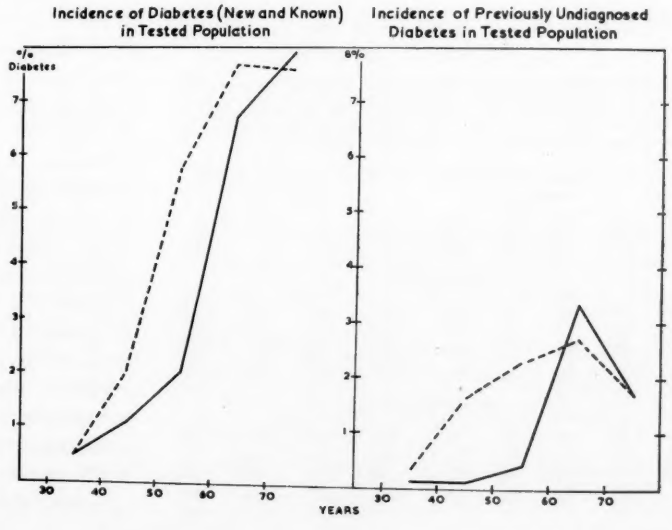

FIGURE 2 Incidence of diabetes in the tested population (11,092 cases) by age and sex. Key: Males _____ Females .....

where early diagnosis is the rule. Unfortunately, in a case finding study the older age groups are more difficult to reach than the younger groups, in whom diabetes is much less common.

Post-Prandial Blood Glucose Levels in Non-Diabetics Following the Newmarket Survey, the blood glucose levels obtained from all those who were not classified either as diabetic or doubtful diabetic were grouped statistically in an attempt to show the possible influence of such factors as age, sex, time interval following meal, and the nature, (but not the content of the meal) eaten. The results are summarized in Table 7. It should be remembered that all blood specimens were capillary in origin and were estimated by a method giving true blood glucose levels. The main conclusions from this table are: 1) In most instances the mean blood glucose level was below rather than above 100 mgm. per 100 cc. 2) Mean values were slightly higher following lunch than they were after breakfast. 3) No definite differences between the levels could be noted between males and females. 4) Relatively small differences could be attributed to the time interval following the meal. There was a slight, but not always consistent, tendency for the level to fall as time interval increased. Often this fall was more noticeable after the two-hour period. 5) Age appeared to exert little or no influence except in the eldest group—from sixty years up. Here a slight increase in the mean value was usually observed.

In general, the table is striking for the absence of any marked pattern of variation with the factors tabulated. It might well be expected that the mean values for the blood sugar would parallel a normal glucose tolerance curve, with a definite peak at between one half and one hour following the meal. However, this tendency is not well shown in the figures in this table. Perhaps this is because the curve following a normal meal is a flat one, or perhaps a small, but definite, peak occurs, but at such a variable interval in different individuals eating different meals, that the true picture is obscured in a composite table such as this. It is unfortunate that there were too few observations on fasting specimens to include them in this table.

TABLE 7 Mean Capillary Blood Glucose Values (mg. per 100 cc.) in Nondiabetics. (Newmarket Survey)

NOTE: 3,885 separate observations from persons classified as nondiabetic comprise the data for this table. Mean blood glucose levels have been grouped according to the meal, time following the meal, age and sex. The standard deviation of each mean, which is not shown because of limited space, ranged from 11 to 34 mg. per 100 cc.

Age Groups	Time Following Breakfast (Minutes)				Time Following Lunch (Minutes)			
In Years	30-59	60-89	90-119	120-149	30-59	60-89	90-119	120-149
A. MALES								
0-19	88	86	84	85	103	102	105	90
20-39	93	87	83	74	101	100	97	88
40-59	92	88	96	89	108	111	104	94
60-	96	98	97	86	116	112	118	92
B. FEMALES								
0-19	90	88	79	76	103	98	96	88
20-39	87	83	80	81	100	94	91	92
40-59	94	88	88	83	104	103	98	94
60-	104	92	96	80	115	107	103	101

CONCLUSIONS

The prevalence of diabetes in the population tested in these two surveys is similar to that found in Newmarket.[1] Indeed, the incidence of diabetes, expressed as a percentage of the population tested in each of the three towns, Newmarket, South Porcupine and Hawkesbury was remarkably constant; all diabetics, 1.27; 1.33; 1.28; new diabetics, 0.52; 0.54; 0.51; known diabetics, 0.75; 0.79; 0.77. This similarity occurred in spite of the different racial and national composition of the three towns. The largest groups tested—French and British—each contained 1.3% diabetics.

In any survey, the technical methods employed and the screening and diagnostic criteria selected have an important bearing on the number of diabetics revealed. When lower diagnostic blood sugar levels are set, the number of diabetics found will be larger. This consideration, together with other variable factors, should be borne in mind when attempting to compare the results of the many surveys and detection drives now published in the literature. Concerning technic, the following factors which can influence results may be listed: 1) the screening method—urinalysis or blood sugar estimation or both; 2) the blood sugar method—true glucose estimation, or total reducing substances; 3) the origin of blood samples—venous or capillary; 4) the timing of tests in relation to meals—fasting or post-prandial; 5) the diagnostic criteria for diabetes; 6) the type of glucose tolerance test and the method of interpretation of results; 7) the relative efficiency in following up all the persons with initial abnormal results, so that a diagnosis can be established in every case. Concerning the population tested, certain other considerations arise. It is important, for example, to know the age and sex distribution of the population and the method of selection, if any, of those tested from among the whole group.

Blotner and Marble[7] have reviewed recent diabetic

case finding studies in the United States. Included are several important diabetes detection programs. Such studies have been reported by Ford[8] (Jacksonville, Fla.), Harting and Glenn[9] (Brookline, Mass.), MacBryde[10] (St. Louis, Mo.), and Sharkey[11] (Dayton, Ohio), as well as by others from Minnesota and Milwaukee, Wis.[12, 13] These surveys were planned primarily as case finding projects and not as statistical studies of the incidence of diabetes. They were carried out in large centers of population, which enabled large numbers to be screened quickly, but did not permit a large proportion of the population to be covered by the survey. As an extreme example of how selection may operate in a group tested in a large city, the results of the testing station in the Diabetes Fair in Boston are of interest. Among 2,215 persons tested, more than half of the total showed either glycosuria or hyperglycemia. Clearly, this does not detract from the usefulness of this type of survey to the community, but it does limit the value of any deductions made concerning the prevalence of diabetes in the community as a whole.

SUMMARY

Data concerning the prevalence of diabetes in two Ontario towns are presented. A total of 6,673 persons were tested for diabetes. In the first town 70 per cent and in the second, 60.5 per cent of persons over the age of six years were included in the survey.

Postprandial capillary blood and urine samples were tested for glucose from all persons seen in the survey.

Eighty-seven diabetics (1.3 per cent of the population tested) were encountered. Thirty-five (0.52 per cent) of these were previously undiagnosed and 52 (0.75 per cent) were known diabetics.

In certain age groups—women from 50 to 69 years and men from 60 to 69 years—over 6 per cent of those tested were diabetic.

The prevalence of diabetes was essentially the same in both the French and British groups tested.

Glycosuria, of both diabetic and nondiabetic origin, occurred in 1.7 per cent of 11,092 persons examined.

The mean blood glucose values in 3,885 nondiabetics tested in a previous survey are presented.

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Incidence of Peripheral Vascular Changes In Diabetes Mellitus

A SURVEY OF 264 CASES

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The advent of insulin and widespread knowledge of its application in the treatment of diabetes mellitus has shifted the emphasis from the more dramatic aspects concerned with immediate preservation of life to the challenge of so-called "complications." The increase of these complications seems to bear direct relationship to the fact that the life span of diabetics has been prolonged. Joslin and his group[1] emphasize that, as a cause of death, arteriosclerosis in its different manifestations has risen threefold since the days of Naunyn, while coma has dropped to one-twentieth of its former incidence. Marble[2] points out that while prior to 1914, 63.8 per cent of diabetics died in coma, this cause of death was reduced to 3.1 per cent by 1946; at this time he found 66.6 per cent out of 651 diabetic deaths to be due to arteriosclerosis in one form or another.

A number of factors suggested themselves as possibly related to the incidence of various manifestations of vascular disease in diabetes. The most important of these seemed to be: the duration of disease, the age of onset, obesity, hypertension, the control of diabetes, and familial history of diabetes.[3–10] Evaluation of these factors might help in answering the basic question, "What is the relation of diabetes to vascular disease?" Three possibilities have been suggested by Ricketts:[4] 1.) Vascular disease might cause diabetes. 2.) Diabetes might cause vascular disease. 3.) Some common factors might cause both the diabetes and the changes in the blood vessels. No acceptable evidence of the first theory has been brought forward so far to our knowledge.[11] Whether the second or third possibilities offer the most logical explanation is still a wide open question.[1, 7, 9, 12, 13] It is hoped that the data presented may shed further light on the relationship of some of the above enumerated factors to the development of peripheral vascular changes in diabetes.

METHODS AND MATERIAL

For this survey, a study was made of 264 patients with diabetes, including females. (Table 1). The youngest individual was 17 years of age, the oldest 64: about 70 per cent were between 20 and 40 years of age. The material was grouped according to age (Tables 2, 3, 4, and 5), according to duration of disease (Table 6), and according to degree of control of diabetes (Tables 1, 2, 3, 4, and 5).

Checked and listed were the following data: obesity, hypertension, eye-ground changes (Keith-Wagener classification,[14]) changes in the color of the extremities

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related to posture, peripheral pulsations, hypercholesterolemia, calcification of the arteries in lower extremities, skin temperature of the toes, oscillometric readings (listed if below accepted normalcy), electrocardiographic abnormalities, incidence of acidosis, albuminuria and a family history of diabetes. The results are shown in the tables.

COMMENTS

The figures presented permit the following comments on the incidence of peripheral vascular disease in diabetics and on the six factors which have been considered as of possible importance for the incidence of vascular disease:

Duration of disease Roughly 30 per cent of the patients showed some evidence of relative peripheral arterial insufficiency within five years. This percentage does not increase significantly within the succeeding five years; it rises above 52 per cent within fifteen years and still somewhat higher within 25 years. The majority of cases surveyed here fall within the five-and ten-year duration groups; it might be argued that comparison with a small group of cases with longer duration of disease somewhat diminishes that significance of percentage figures. On the other hand, it will be noted that all age groups are represented within the five and ten year duration groups, while the groups with duration of more than 15 years do not include a single individual below 40 years of age. Taking into account the well known fact that the incidence of obliterating arteriosclerosis of the lower extremities increases with age,[15, 16, 17, 18] it appears obvious from the figures presented that the incidence of relative peripheral arterial insufficiency of the lower extremities is surprisingly high in cases with only up to 5 years' known duration of diabetes.

Obesity Essentially the figures bear out the known fact that the incidence of obesity in diabetes is high[1, 10, 19]. It is of interest to find such a high percentage in young diabetics. While there were 24.3 per cent hypertensives in the whole group of 264, there were 43 per cent hypertensives among the obese. The figures concerning the incidence of peripheral vascular damage show no essential difference between the obese and the nonobese.

Age of Onset The majority of patients had the onset of diabetes in early adult life. This fact might bear relationship to the high incidence of signs of relative peripheral arterial insufficiency in this group.[7, 9]

Hypertension Survey of this group confirms the established fact that hypertension is fairly common among

TABLE 1 Data in Cases of Diabetes Ages 17-64

Control	Good	Fair	Poor	Total	Per Cent
Number of Cases	109	71	84	264	
Obesity	44	23	33	100	37.9
Hypertension	31	14	19	64	24.3
A.S.R. K.W. I and II	25	17	23	65	24.6
A.S.R. K.W. III and IV	4	2	7	13	4.9
Postural Color Changes	26	31	30	87	33
D.P. and/or P.T. Absent Bilat.	30	19	18	67	25.4
Hypercholesterolemia	10	9	12	31	11.7
Calcif. L.E.	20	17	20	57	21.6
Toe Temp. Below Room Temp.	4	3	5	12	4.5
O.R. Below Accepted Norm.	10	13	13	36	13.6
Abnormal E.C.G.	7	11	8	26	9.9
Severe Acidosis	6	9	11	26	9.9
Albuminuria	3	0	4	7	2.7
Familial History	33	22	17	72	27.3

Key: A.S.R., Arteriosclerotic Retinopathy; K.W., Keith Wagener; D.P., Dorsal Pedal; P.T., Posterior tibial; Calcif., Calcification; L.E., Lower Extremities; Temp., Temperature; O.R., Oscillometric readings; E.C.G., Electrocardiogram

TABLE 2 Data in 92 Cases of Diabetes Ages 17-30

Control	Good	Fair	Poor	Total	Per Cent
Number of Cases	34	23	35	92	
Obesity	5	5	6	16	17.4
Hypertension	4	0	3	7	7.6
A.S.R. K.W. I and II	2	2	4	8	8.7
A.S.R. K.W. III and IV	0	0	2	2	2.2
Postural Color Changes	9	9	9	27	29.3
D.P. and/or P.T. Absent Bilat.	10	5	4	19	20.7
Hypercholesterolemia	3	0	3	6	6.5
Calcif. L.E.	3	1	1	5	5.4
Toe Temp. Below Room Temp.	1	1	0	2	2.2
O.R. Below Accepted Norm.	2	3	0	5	5.4
Abnormal E.C.G.	0	2	0	2	2.2
Severe Acidosis	4	3	5	12	13.0
Albuminuria	1	0	2	3	3.3
Familial History	10	6	5	21	22.8

TABLE 3 Data in 105 Cases of Diabetes Ages 30-40

Control	Good	Fair	Poor	Total	Per Cent
Number of Cases	47	28	30	105	
Obesity	21	8	15	44	41.9
Hypertension	16	5	7	28	26.7
A.S.R. K.W. I and II	15	11	10	36	34.3
A.S.R. K.W. III and IV	1	0	1	2	1.9
Postural Color Changes	9	13	10	32	30.8
D.P. and/or P.T. Absent Bilat.	10	5	5	20	19.1
Hypercholesterolemia	4	7	4	15	14.3
Calcif. L.E.	7	3	7	17	16.2
Toe Temp. Below Room Temp.	1	2	1	4	3.8
O.R. Below Accepted Norm.	4	5	3	12	11.4
Abnormal E.C.G.	3	3	2	8	7.6
Severe Acidosis	2	5	4	11	10.5
Albuminuria	1	0	0	1	1.0
Familial History	11	8	8	27	25.7

diabetics.[1, 10, 20, 21] It is striking to find that of 64 hypertensive diabetics, 23 had signs of relative peripheral vascular insufficiency. The distribution among the age groups shows that out of 35 hypertensive diabetics between 17 and 40 years of age, 13 (37.1 per cent) had signs of peripheral vascular damage, while out of 29 hypertensive diabetics between 40 and 64 years of age, 15 (51.7 per cent) had such signs. (Table 7) Figures concerning incidence of peripheral arterial insufficiency in nondiabetic hypertensives are not available at present; it is our impression that we have rarely encountered signs of occlusive vascular disease in the lower extermities of nondiabetic hypertensives in the younger age group.

Control of diabetes Under the present mode of treatment nothing close to ideal control (which would approach the physiological conditions) seems possible; prolonged control with a normal blood sugar curve and freedom from glycosuria was not obtainable in our group. We should always talk about "different degrees of uncontrol" as Lawrence[22] so aptly expressed it.

Joslin[1] permits glycosuria amounting to 7 per cent of the carbohydrate intake with the upper level of 10 per cent of the total ingested. Mosenthal follows about the same pattern. Duncan,[23] in a personal communication, stated that good control would mean having fasting and postprandial blood sugar within normal limits or with a mild degree of hyperglycemia occasionally, and glycosuria only appearing at infrequent intervals over a long period of time. Tolstoi[24] and Dolger[25] are guided by clinical control, watching the patient's weight, subjective well being, and absence of acidosis.

The degree of control in this group has been determined on the basis of an overall survey and not on one single examination. The criteria chosen are arbitrary and as such open to criticism. This is the definition of the criteria used:

Good Control: Urinary excretion of glucose not exceeding 10 per cent of the carbohydrate intake, frequent medical check-up, strict adherence to diet, subjective feeling of well-being, maintainance of adequate weight, frequent urine examinations, immediate consultation with the physician if any metabolic derangements are noted, fasting blood sugar values not above 150 mg. per 100 cc. (180 mg. in older age groups).

Fair Control: Urinary glucose up to 25 per cent of the carbohydrate intake, infrequent medical check-up, occasional laxity in adherence to diet, no weight loss, irregular urine examinations, fasting blood sugar values between 150 and 250 mg. per cent.

Poor Control: Urinary glucose over 25 per cent of carbohydrate intake, rare medical check-up, intermittent loss of weight, lack of energy, etc., laxity in adherence to diet and insulin, incidence of acidosis, fasting blood sugar values over 250 mg. per 100 cc.

Our figures, by themselves, would not indicate that the degree of control of diabetes was a factor in the development of peripheral vascular disease. There might be some suggestive evidence of high incidence of retinal hemorrhage in the poor control group (12 per cent) compared to the good control group (3½ per cent). The other vascular manifestations are about evenly distributed among "good", "fair", and "poor" control groups.

It has been shown recently,[26] that alloxan—diabetic dogs can be kept free from vascular complications by rigid control for over two years. While of course alloxan diabetes cannot be unqualifiedly compared with spontaneous diabetes mellitus in man the above observation remains of great importance.

TABLE 4 Data in 34 Cases of Diabetes Ages 40-50

Control	Good	Fair	Poor	Total	Per Cent
Number of Cases	15	11	8	34	
Obesity	9	3	6	18	53.0
Hypertension	5	3	4	12	35.3
A.S.R. K.W. I and II	2	1	1	4	11.8
A.S.R. K.W. III and IV	2	0	3	5	14.7
Postural Color Changes	3	6	7	16	47.1
D.P. and/or P.T. Absent Bilat.	4	4	3	11	32.4
Hypercholesterolemia	1	1	3	5	14.7
Calcif. L.E.	1	4	5	10	29.4
Toe Temp. Below Room Temp.	1	0	1	2	5.9
O.R. Below Accepted Norm.	2	1	5	8	23.5
Abnormal E.C.G.	1	2	3	6	17.7
Severe Acidosis	0	0	1	1	2.9
Albuminuria	1	0	1	2	5.9
Familial History	7	5	1	13	38.3

Key: A.S.R., Arteriosclerotic Retinopathy; K.W., Keith Wagener; D.P., Dorsal Pedal; P.T., Posterior tibial; Calcif., Calcification; L.E., Lower Extremities; Temp., Temperature; O.R., Oscillometric readings; E.C.G., Electrocardiogram

TABLE 5 Data in 33 Cases of Diabetes Ages 50-64

Control	Good	Fair	Poor	Total	Per Cent
Number of Cases	13	9	11	33	
Obesity	9	7	6	22	66.7
Hypertension	6	6	5	17	51.6
A.S.R. K.W. I and II	6	3	8	17	51.5
A.S.R. K.W. III and IV	1	2	1	4	12.1
Postural Color Changes	5	3	4	12	36.4
D.P. and/or P.T. Absent Bilat.	6	5	6	17	51.6
Hypercholesterolemia	2	1	2	5	15.2
Calcif. L.E.	9	9	7	25	75.8
Toe Temp. Below Room Temp.	1	0	3	4	12.1
O.R. Below Accepted Norm.	2	4	5	11	33.7
Abnormal E.C.G.	3	4	3	10	30.6
Severe Acidosis	0	1	1	2	6.1
Albuminuria	0	0	1	1	3.0
Familial History	5	3	3	11	33.7

TABLE 6 DATA IN CASES OF DIABETES, GROUPED ACCORDING TO DURATION OF THE DISEASE.

Duration	Number of Cases	Age Group	Obesity	Hypertension	A.S.R. K.W. I and II	A.S.R. K.W. III and IV	Postural Color Ch'ge	D.P. and/or P.T. Absent Bilat.	Hypercholesterolemia	Calcif. L.E.	Toe Temp. Below Room Temp.	O.R. Below Accepted Norm	Abnormal E.C.G.	Severe Acidosis	Albuminuria	Familial History
Up to 5 years	85	17-30: 51.8% 30-40: 34.1% 40-50: 5.9% 50-64: 8.2%	34 40%	22 25.9%	18 22.2%	1 1.2%	28 32.9%	17 20%	8 9.4%	13 15.3%	3 3.5%	11 12.9%	7 8.2%	6 7.1%	1 1.2%	21 24%
5-10 years	162	17-30: 29.6% 30-40. 46.3% 40-50: 15.4% 50-64: 9.6%	55 33.9%	33 20.4%	41 25.3%	7 4.3%	53 32.7%	42 25.9%	19 11.7%	33 20.4%	8 4.9%	20 12.3%	13 8%	17 10.5%	3 1.8%	44 27.2%
10-15 years	11	17-30: 0% 30-40: 9.1% 40-50: 27.3% 50-64: 63.6%	6 54.5%	6 54.5%	4 36.4%	3 28.3%	2 18.2%	6 54.5%	3 28.3%	7 63.6%	1 9.1%	2 18.2%	4 36.4%	2 18.2%	2 18.2%	5 45.5%
15-20 years	1	17-30: 0% 30-40: 0% 40-50: 0% 50-64: 100 %	1 100%	0	0	0	1 100%	0	0	1 100%	0	0	0	0	0	0
20-25 years	5	17-30: 0% 30-40: 0% 40-50: 20 % 50-64: 80 %	4 80%	2 40%	2 40%	2 40%	3 60%	2 40%	1 20%	3 60%	0	3 60%	2 40%	1 20%	1 20%	2 40%

Key: A.S.R., Arteriosclerotic Retinopathy; K.W., Keith Wagener; D.P., Dorsal Pedal; P.T., Posterior tibial; Calcif., Calcification; L.E., Lower Extremities; Temp., Temperature; O.R., Oscillometric readings; E.C.G., Electrocardiogram

One anticipates with interest the results of experimental investigation indicated by Ricketts[27] where groups of well controlled and poorly controlled diabetic dogs will be compared. In the presence of so many as yet unclarified metabolic factors seemingly associated with development of vascular disease, it is reasonable and logical to strive for as good a control as we possibly can.

Wilson, Root, and Marble[28] reported recently on 247 cases in which diabetes started early in life; they found that in those kept under excellent control there was absence of advanced vascular changes after periods of 20 to 34 years. The incidence of severe vascular changes was high in those with fair or poor control. If their mode of control could be duplicated in a large scale investigation, an answer to the basic question might be obtained.

TABLE 7 Incidence of Peripheral Vascular Changes in Hypertensive Diabetics

Type of Group	Number of Patients	Incidence of Peripheral Vascular Changes
Total group of diabetics	264	154 (58.4%)
Hypertensives	64	41 (65.4%)
Hypertensives (17-40 yrs. of age)	35	16 (45.8%)
Hypertensives (40-64 yrs. of age)	29	25 (86.2%)

Familial history of diabetes Except for a higher incidence of obesity (51.4 per cent, compared to 37.9 per cent), there were no significant differences between patients with a history of diabetes in the family and those without such history.

The most remarkable fact gathered from the figures of this survey is the enormously high incidence of signs of relative arterial insufficiency in young diabetics (Table 7). If more attention were paid to those early signs (especially postural color changes), some of the irreversible sequelae might be avoidable. It is suggested that all diabetics regardless of age and regardless of presence or absence of complaints referable to the lower extremities, be carefully examined and frequently checked for the early signs of arterial insufficiency. If such signs are found, a strict peripheral vascular routine should be instituted and maintained even in complete absence of subjective symptoms.

SUMMARY

In 264 cases of diabetes the search was made for relative arterial insufficiency in the lower extremities. In 58.4 per cent of the 197 patients below 40 years of age about 50 per cent showed such changes. The duration of diabetes and the degree of control, obesity, and hyper-

tension are possible factors influencing the development of vascular damage.

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Neurogenic Bladder Dysfunction as a Complication of Diabetes

REPORT OF SEVEN CASES

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It was first pointed out by Marchal de Calvi,[1] quoting a case of Le Bret, in 1864 that diabetes can cause neurological disturbances affecting the bladder. Subsequently, cases of dysfunction were reported by Bonardi (1897)[2] and Williamson (1898).[3] Naunyn (1906)[4] and Von Noorden and Isaac[5] stated that urinary difficulties may be found in cases of diabetes although they did not mention any cases of their own. Caulk, Greditzer, and Barnes (1919),[6] in their study of the urological findings in 500 cases of diaseases of the central nervous system, and Lendrum and Moersch ,(1934),[7] in their study of 250 cases of "cord bladder", did not mention one instance of associated diabetes mellitus.

In reviewing the literature, it appears to us that Bowen and Aaron (1926)[8] were the first to diagnose and recognize in life that the presence of a "cord bladder" in one of their patients was probably due to the diabetes since there was no evidence of either syphilis or pernicious anemia. In this case, degeneration of the posterior columns was found at post mortem. McKittrick and Root (1928)[9] mentioned that they had seen 3 cases of bladder paralysis in diabetics in whom no general or local cause was found. Since that time a growing number of publications have reported or mentioned cases of bladder paralysis.[10-26] In 1935, when Jordan and Crabtree[12] reviewed the literature and reported 7 cases, bladder paralysis was definitely established as a complication of diabetes mellitus.

In 1940, Emmett[26] introduced transurethral resection for luetic "cord bladder". In 1947,[27] he reported a group of cases of "cord bladder" treated successfully by this method; among the group was a case of diabetes. Use of this procedure was later reported by Lich and Grant (1948),[28] in 2 cases of diabetes, by Swarts and Stein (1948)[24] in one case, by Emmett, Daut and Sprague (1949)[29] in 3 cases (see Table 1), and by Fineman, Ferber, and Roginsky (1952)[39] in two cases.

THE CLINICAL PICTURE

The etiology of neurogenic dysfunction of the bladder of diabetics is still unknown. One of the prevailing theories is that arteriosclerosis of the small nutrient vessels to the nerves, especially to the peripheral portions of the latter, is responsible for the neuropathy (Woltman and Wilder, 1928).[30] This was supported by the post mortem findings in the case of Zukor and Marder (1952).[36] Jordan, Randall and Bloor (1935)[31] found a reduction of fat content of the nerves of amputated legs of diabetics. They believed that, in poorly controlled diabetics, the excessive oxidation of fat to meet the energy requirements may lead to peripheral demyelinization of the nerves. Rudy (1945)[33] stated that diabetic

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TABLE 1 Cases of Bladder Paralysis Encountered in the Literature

Author	Year	Number
Bowen and Aaron	1926	1
McKittrick and Root	1928	3
Czoniczer	1928	1
Root	1933	2
Jordon and Crabtree	1935	7
Sharkey and Root	1935	1
Jordon	1936	5
Sheppe	1936	2
Gill	1936	2
McClellan	1939	1
Baldwin and Root	1940	3
Rudy and Muellner	1941	3
Rudy and Epstein	1945	11
Rundels	1945	18
Campos and Coledrero	1947	6
Emmet	1947	1
Swarts and Stine	1948	1
Lich and Grant	1948	2
Emmett, Daut and Sprague	1949	3
De Jong	1950	1
Zucker and Marder	1952	1
Rabinowitch	1952	2
Fineman, Ferber and Roginsky	1952	2
Spring and Hymes	1953	7

neuropathy is a manifestation of a diffuse disturbance that may invade the entire nervous system, resulting from vitamin B Complex deficiency. Experiments by Zimmerman and Burach[34] showed that extensive demyelinization occurs in the sciatic, median and vagus nerves of dogs fed a vitamin B deficient diet. Needles,[35] on the other hand, found no lack of sufficient vitamin B in his study of patients with diabetic neuritis. The whole matter was well summed up by DeJong in 1950:[25] "It is probable that neither a primary, nor a conditioned thiamine deficiency, nor occlusive vascular disease is alone responsible for the difficulty and it may be that the peripheral nerve changes result from abnormalities of metabolism, usually in chronic, unregulated diabetes."

There is no predilection as regards age and sex, though it appears to be more frequent in the older diabetic. It is seldom, if ever, seen in the very young diabetic due to the incomplete laying down of myelin. Experimentally, avitaminotic neuritis does not occur in nerves that are not completely myelinated.[38]

Diabetic dysfunction of the bladder is often overlooked. The diabetes may be mild or severe, usually it has been poorly controlled or untreated. An acute exacerbation of the diabetes, an infection, or an operation may act as precipitating factors. Urinary disturbances are insidious in onset and often receive little attention until well advanced. Vesical dysfunction may vary in duration from one month to more than 25 years. The incidence of vesical dysfunction is about 1 to 2 per cent.

The early recognition and treatment of this complication should be aided by knowledge of the salient features. The earliest symptom is difficulty in emptying the bladder, especially when the patient is confined to bed. The interval between attempts at urination may become prolonged. Then there is hesitation, straining, weakness of the stream, a sensation of incomplete emptying of the bladder and urgency and incontinence. These symptoms may occur with or without residual urine. Overdistension of the bladder frequently causes the patient to consult a physician because of an abdominal tumor. When urinary infection supervenes, frequency, dysuria, and urgency ensue. The infection may spread rapidly and become fatal. On cystoscopic examination there is found increased bladder capacity, diminshed bladder sensation and fine trabeculation. In some cases, immobility of the internal sphincter may be the only abnormality found. On cystometric examination, there may be impaired or absent sense of filling, very low expulsive force and an increased bladder capacity. Residual urine varies from nothing to over 300 cc. Uninhibited bladder contractions do not occur. Clinical improvement usually precedes improvement of the cystometric curve; as the improvement continues, it is frequently reflected by the change in the cystometric curve which approaches normal.

The spinal fluid protein is frequently elevated. There may be a left or a mid-zone rise of the colloidal gold curve.[29, 32] The gastric juice is normal in its hydrochloric acid content.

Neurogenic bladder dysfunction related to diabetic neuropathy must be differentiated by clinical study and laboratory observations from that caused by tabes dorsalis, pernicious anemia, spinal cord tumor, transverse myelitis, arteriosclerosis and trauma to the spinal cord.

TREATMENT

The treatment of the diabetic "cord bladder" includes metabolic and urologic measures. The former consists of control of the diabetes with diet and insulin. The value of treatment with vitamins and pregnant mammalian liver extract is yet to be determined.[37] The urologic treatment consists of prevention and treatment of infection, reduction of residual urine and perservation of muscle tone, and restoration of normal function.

Since the introduction of modern chemotherapy and antibiotic treatment, infections of the urinary tract in neuro-muscular disease have become less serious. Such treatment, selected specifically depending on the causative organism, must be supplemented by the use of a continuous indwelling catheter in the urethra. Catheter

drainage need no longer be feared; in fact it is mandatory in order to maintain free drainage without which infection is certain. If the urine is sterile, the antibiotics are used prophylactically.

The early relief of urinary retention and the maintenance of free drainage, temporarily, by continuous indwelling catheter will generally prevent the severe or even irreparable damage certain to follow days or weeks of prolonged urinary retention, with or without infection. The bladder and kidneys are thus spared prolonged over distention leading to increased atony of the bladder and hydronephrosis. Catheter drainage should be continuous; intermittent drainage is not adequate and furthermore frequent catheterization needed for decompression of the bladder may result in epididymitis and prostatitis, as well as trauma to the deep urethra.

After about 10 days of catherization, the catheter can be removed and the patient allowed to void. He is encouraged to make an attempt every 3 hours, assisted by standing, and by using manual pressure (by the method of Crede); he is also given parasympathomimetic drugs such as Furmethide, Urocholine, and Doryl. If the patient is able to void, the residual urine is checked daily. If the amount is over 150 cc., without evidence of becoming less, surgical treatment is needed.

Transurethral resection of the entire circumference of the vesical neck is the surgical procedure in both males and females. The mechanical weakening of the bladder outlet, which is not atonic, will then enable the hypotonic or atonic bladder to empty itself, aided if necessary by abdominal straining or manual compression. In addition to the added vesical expulsive force which abdominal straining produces, by increasing the intracystic pressure, the stretch reflex is variably stimulated.

Older men may have both neurogenic vesical dysfunction and prostatic obstruction. In some cases accurate differentiation may not be possible, but this is not important because the treatment in either case is the same.

If there is a large volume of residual urine after operation it must mean that an insufficient amount of tissue has been removed from the bladder outlet; further removal of tissue by transurethral resection is indicated. In cases of cord bladder in which even repeated resections fail to give relief permanent drainage of the bladder by cystostomy tubes will be needed. Prolonged catheter drainage may lead to posterior urethritis, prostatitis, epididymitis or a urethral abscess.

Needless to say, the resection of the bladder neck must be performed with care. The operation should be done by a man well trained in this urologic procedure, in order to reduce to a minimum complications such as urinary incontinence, which results from cutting the external sphincter, the production of a urethrovaginal fistula by resecting too much tissue in the female, rupture of the bladder by cutting into the bladder, urethral injuries resulting from cutting into the urethral orifice, and hemorrhage.

The early recognition and treatment of bladder atony is extremely important. The presence of residual urine interferes with fractional collection of urine; urinary infections which supervene may make good diabetic regulation impossible; and long standing distention, particularly with infection, may produce permanent bladder and kidney damage. If recognized early, however, and treated well, the condition may remain entirely benign.

CLINICAL OBSERVATIONS

Within the last 3 years we have treated 7 cases of bladder paralysis associated with diabetes. There were 5 women and 2 men. The ages ranged from 20 to 65 years. The diabetes was severe in 3 cases, mild in 4; the duration of the disease was from 9 to 21 years. In 3 cases there was poor control of the diabetes. There had been marked weight loss in 2. The diagnosis of peripheral neuropathy was made in the 3 cases in which a neurological consultation was secured. There was associated bowel atony in 2 cases. The paralysis of the bladder was precipitated by amputation of a limb for gangrene in one case, by a carbuncle infection of the neck in a second patient, and by acidosis in a third.

The residual urine varied from 300 cc. to complete retention. Cystometry showed an atonic curve in all cases. Transurethral resection was performed successfully in 2 cases. Treatment with retained indwelling catheter for 10 days plus administration of antibiotic was successful in 2 other cases. The patients were then able to void normally and there was little residual urine remaining in the bladder. One patient had hemorrhagic cystitis and acute retention of urine. Indwelling catheter drainage was unsuccessful in that the hemorrhage continued. Cystotomy was done in order to control the hemorrhage, but was unsuccessful; the patient died because of continued hemorrhage and infection of the urinary tract. In one case, because of a cerebrovascular disorder, and in another because of a chronic renal infection, urologic surgery could not be undertaken because of the high operative risk.

CASE REPORTS

Case 1: Neurogenic bladder dysfunction treated successfully by transurethral resection of the neck of the bladder..

A woman, aged 58 years, was admitted to the Bronx Hospital on February 21, 1948. She had diabetes controlled with 40 units of protamine zinc insulin. For 2 weeks she had had diarrhea with frequent stools, numbering up to 30 daily. She also complained of difficulty in voiding and incontinence of urine; there was marked abdominal distention.

It was found that she had a distended bladder which could be felt above the pubis; on catheterization, 1500 cc. of cloudy urine were withdrawn. The neurological examination showed depressed knee and ankle reflexes. By cystoscopy, diffuse low-grade cystitis was noted. The sphincter of the bladder was contracted concentrically. Pyelography showed bilateral hydronephrosis of slight degree. X-ray examination with a barium enema showed atony and dilatation of the colon; it was felt that she had disturbances of both the function of the bladder and the colon as a result of diabetic neuropathy.

A circumferential resection of the neck of the bladder was performed without difficulty. Afterwards she was able to void with ease and no residual urine was found in the bladder.

Case 2: Neurogenic bladder dysfunction also relieved by transurethral resection of the bladder neck.

A woman, 65 years of age, was admitted to the Bronx Hospital on October 11, 1948. She had had diabetes for 10 years and had been receiving 80 units of protamine zinc insulin daily. She was admitted to the hospital because of gangrene of the right leg; it was necessary to perform an emergency operation to amputate the limb in the mid thigh. Seventeen days after the operation she had difficulty in voiding; it was found that the residual urine measured 2500 cc. Continuous drainage of the bladder by catheter was carried on for 10 days. During this period she was given penicillin and streptomycin. Cystometric studies showed that she had atony of the bladder.

A circumferential resection of the neck of the bladder was preformed. About one week after the operation, when the Foley catheter was removed, she was able to void with ease. The bladder contained only 100cc. of residual urine.

Case 3: Recovery from neurogenic bladder dysfunction secondary to diabetic neuropathy following good control of the diabetes and continuous catheter drainage.

A man, aged 25, was admitted to the Bronx Hospital on February 14, 1952, because of diabetic acidosis which had necessitated hospitalization on seven previous occasions. He was in a semi-comatose state and showed Kussmal type of breathing. The blood sugar was 350 mg. per 100 cc. The urine contrained sugar graded 3 plus and acetone graded 4 plus; microscopic examination showed about 50 white blood cells in each high power field. The blood urea nitrogen was 12 mg. per 100 cc.

Treatment of the diabetic acidosis with insulin and other measures brought about recovery but he had difficulty in emptying his bladder. The residual urine measured 100 cc. Cystometric studies showed the typical atonic curve. The neurologic examination showed absence of the knee jerks, absence of vibration sense in the lower extremities, and marked loss of sensation to pain and temperature below the level of the tenth-thoracic segment. Continuous drainage of the bladder was administered for 10 days. His diabetes was brought under control and the diabetic regimen was supplemen ted by the administration of vitamins orally and parenterally. The neurologic signs subsided and his bladder function improved. There was absence of residual urine after removal of catheter and he was able to void without difficulty.

Case 4: Bladder dysfunction appearing while diabetes was uncontrolled relieved after a short course of diabetic management together with continuous drainage provided by catheter.

A 42-year-old man was admitted to the Bronx Hospital on February 18, 1951. He complained of frequent urination occuring about every hour and nocturia occurring 5 or 6 times each night. These symptoms were accompanied by urgency, strangury, and episodes of gross hematuria of a months duration. It was found that he had 150 cc. residual urine. On cystoscopy it was noted that he had marked inflamation of the mucosa of the bladder and edema of the bladder neck. Cystometry showed an atonic curve. The urine contained 5 per cent sugar. Microscopic examination showed many leucocytes and erythrocytes in each high power field.

The neurologic examination showed diminished knee and ankle jerks and diminshed tactile and thermal sensation below the first lumbar segment.

The diabetes was controlled with 40 units of NPH insulin daily. The diet was supplemented by vitamins given orally and parenterally. Continuous drainage of the bladder was begun. After 10 days of catheter drainage, the urine became clear. The patient was now able to void

with ease and there was no residual urine in the bladder.

Case 5: Difficulty in emptying the bladder because of diabetic neuropathy leading to advanced renal damage and associated infection of the urinary tract. Unsuccessful attempt at treatment by cystotomy.

A woman, aged 61, was admitted to the Bronx Hospital on March 20, 1949. She had had diabetes which had become intensified when she had a carbuncle appear on the back of her neck. Glycosuria could not be controlled with 30 units of protamine zinc insulin given daily. For several weeks, she had had trouble in voiding and complained of abdominal fullness. Gross blood had been seen in the urine.

The cystoscopy revealed severe bullous cystitis; she had 800 cc. of cloudy residual urine. The ureters were not obstructed, but there was a cloudy residue urine of 50 cc. in the pelvis of each kidney (normal is zero). Many red blood cells and pus cells were present in the urine.

The patient was treated by continuous drainage of the bladder by catheter, but because of hematuria with clots of blood appearing in the urine a cystotomy was performed about 2 weeks after admission. She had a septic temperature with uremia. The nonprotein nitrogen of the blood was 100 mg. per 100 cc. on admission. It later rose to 200. The blood sugar was 210. The urine contained 2 per cent sugar. Her condition became worse in spit of treatment including the administration of antibiotics. The output of urine became small with a fixed specific gravity. She died of uremia and sepsis about three months after admission.

Case 6: Long-standing atony of the bladder leading to advanced renal damage making radical treatment hazardous.

A woman, aged 60, was admitted to the Bronx Hospital on March 5, 1950. She had had diabetes for many years, which had been controlled by diet. She had had the left kidney removed because of hydronephrosis with urinary tract infection about a year before. At this time she had had 150 cc. of residual urine.

On admission to the hospital she had 180 cc. of residual urine. There were calculi in the right kidney. The neurologic examination was negative except for diminished knee and ankle jerks. The urine contained many pus cells. The nonprotein nitrogen of the blood was 30 mg. per 100 cc. The culture of the urine showed the presence of b. coli.

Treatment including the drainage of the bladder by catheter and administration of terramycin brought about slow improvement of her condition. Her temperature subsided and the pain became less. The catheter was removed within two weeks. She was then able to void with only a little difficulty. There was no residual urine in the bladder. At home she continued to get along reasonably well, but there was 4 ounces of residual urine in the bladder. It was felt that her condition would make a resection of the bladder neck hazardous.

Case 7: Transurethral operation considered but not undertaken because of the serious cardiovascular condition.

A woman, aged 52, was admitted to City hospital on August 26, 1951. She remained there approximately 12 weeks. She returned on March 27, 1952. She had had hypertensive heart disease and arthritis for about 10 years and diabetes of mild degree for 21 years. The diabetes had been controlled by diet and insulin which had been used intermittently since 1936. Three days before admission to the hospital she became unable to empty the bladder and catheterization was required. The urine was free from glucose and acetone. The same day she became stuporous and hospitalization was advised.

On admission to the hospital the blood pressure was 160/65 and she had paresis affecting the right side. The peripheral joints showed evidence of rheumatoid arthritis.

The laboratory tests showed that the blood urea nitrogen was 12 mg. per 100 cc. and the blood sugar 182. The microscopic examination of the urine showed 5 to 10 red blood cells and 1 to 3 white blood cells in each high power field. There was a trace of albumen and a small amount of glucose graded 2 plus. On admission she had right sided hemi-paresis. Within 24 hours she recovered from the stupor. It was felt that she had a cerebral angio-spasm. In addition it was thought that the urinary retention had resulted from neurogenic bladder dysfunction related to the diabetes. A neurologic examination showed evidence of peripheral neuropathy. The urological examination showed that she had an atonic bladder; on cystometry the first desire to void appeared when the bladder was filled to 800 cc. (normal at abuot 250 cc.) When viewed through the cystoscope the bladder did not show trabeculation; its capacity was 900 cc. The residual urine amounted to 525 cc.

The diabetic treatment included diet and 15 units of protamine zinc insulin daily.

The examination of the spinal fluid on October 15, 1951 showed that the fluid was clear and under normal

pressure. It contained no cells. The Wasserman and Pandy tests were negative. The colloidal gold reaction was 222 110 000. A transurethral resection was contemplated but because of the patient's poor cardiovascular condition was not performed.

When she was seen in the hospital at the time of her second admission in March, 1952, a note on her hospital record stated that bladder control was good but there were no urologic studies to confirm this.

SUMMARY

Neurogenic bladder dysfunction has appeared in certain cases of diabetes mellitus as one of the manifestations of diabetic neuropathy. The etiology of this condition would appear to be the result of arteriosclerosis of the vas nervorum with secondary degeneration of the nerve fiber, predominantly in the posterior columns of the spinal cord. The incidence of vesical dysfunction is about 1 to 2 per cent of all cases of diabetes. There is no predilection as regards sex, age, and severity of diabetes. This condition should be suspected in diabetics with urinary difficulties, especially when there is difficulty in emptying the bladder when there is no evidence of obstruction. The diagnosis can be made if neurological examination shows evidence of neuropathy and if urological investigation shows the presence of atony in the bladder.

Treatment of the diabetes by diet and insulin with vitamin supplements is important in dealing with the neuropathy. The urological treatment includes decompression of the bladder by continuous catheter drainage, and the use of appropriate antibiotics to combat the urinary tract infection which tends to occur. Transurethral resection of the bladder neck should be considered if there is inability to void and the presence of residual urine amounting to 150cc. or more after a trial of treatment with catheter drainage.

This report presents seven cases of neurogenic bladder dysfunction in association with diabetes. In two cases transurethral resection of the bladder neck was employed successfully. In two cases there was relief after treatment with continuous catheter drainage. One patient died from urinary tract infection plus uremia, in spite of a cystostomy to improve drainage of the bladder. Two patients left the hospital without adequate therapy because catheter drainage proved inadequate and surgical treatment was contraindicated on account of a severe kidney disease in one case and advanced cardiovascular disease in the other.

Neurogenic bladder dysfunction is probably more common than has been suspected. There has been, perhaps, failure to recognize it because of lack of awareness of this condition. Early recognition and treatment will prevent irreversible changes in the bladder and kidneys with the sequels of urinary tract infection, uremia and death.

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Disaster Feeding

Under the conditions of the usual type of disaster, and according to the general Civil Defense plan, it is unlikely that any one individual will be dependent on emergency feeding for longer than 7 days and in no instance longer than 30 days. Specific nutritional deficiencies will not develop in previously well-nourished individuals within this time. Even those marginally nourished should suffer no ill-effects, if the foods used are primarily natural, normal foods whose composition is as varied as circumstances will permit.

It follows then that calories are the predominant nutritional consideration in feeding this group. The Federal Civil Defense Administration has recommended, for planning purposes, a daily per capita calorie allowance of 2,000-2,200 which will prove adequately for a population of normal age-sex distribution and properly rationed, will allow some margin of safety to provide for the higher allowances needed by special groups.

DIABETICS

Diabetics constitute a special problem in disaster situations. The homeless diabetic would probably be unable to procure his usual diet from the simple and limited rations available. Consequently, it would seem wise to place primary dependence on insulin and a thorough self-treatment education of each patient. This would mean that each diabetic should maintain a reserve stock of insulin and extra syringes and needles to administer it. Diabetics who are injured also pose special problems. Knowledge as to the existence of diabetes could be quite important particularly in those with burns or wounds likely to become infected. The unconscious injured diabetic is an obvious problem. These considerations have led to various proposals for identifying the diabetic by a card or identification tag of some sort which would be carried at all times. The problem of diabetics under emergency conditions has been carefully and comprehensively considered by the American Diabetes Association. Butler has reviewed the special problems of diabetics in disasters as well as many other special mediconutritional problems in disaster situations.

From *Disaster Feeding*, by James M. Hundley, M.D., in *The Journal* of the American Medical Association, April 18, 1952.

Serum Cholesterol In Juvenile Diabetes

Serial Determinations in Cases of Recent Onset

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With the technical assistance of
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A high percentage of juvenile patients who have had diabetes for ten to fifteen years are known to be developing serious vascular disease,[1-11] although these patients are in an age group not expected to develop clinically significant vascular degenerative changes. Lipid metabolism as well as carbohydrate metabolism is being emphasized in the study of diabetic patients because of the known relationship between altered lipid metabolism and atherosclerosis. Previous studies at this clinic indicate that vascular changes develop in juvenile diabetic patients in relation to the degree of control of the disease.[10] At this clinic we are undertaking further studies of the interrelationship of degree of diabetic control, level of serum lipids and vascular degeneration. In this present study we are analyzing the serial serum cholesterol observations made during the first and second years after onset, inasmuch as the degree of control of the disease changes rapidly after institution of therapy, and because it is less difficult to assess accurately the degree of control of the disease early in its course. Our objective is to determine changes in the levels of serum cholesterol in relationship to changes in degree of control of the disease.

Hyperlipemia in diabetic patients was observed by Helmont[12] in the seventeenth century and by Dobson[13] in the eighteenth century. Joslin, Bloor and Gray[14] demonstrated the presence of hypercholesterolemia in patients with diabetes mellitus in 1917.

Rabinowitch,[15] White and Hunt,[16] and Chaikoff, Smyth and Gibbs[17] have reported that children with controlled diabetes mellitus have normal serum cholesterol values. In 1942, Butsch,[18] working in this clinic, determined the various fractions of the serum lipids of diabetic patients in varying degrees of control and reported similar observations. She found that the only group in which serum lipid and serum cholesterol values were comparable to nondiabetics were those maintaining good to excellent control. Serum cholesterol values varied somewhat more consistently with degree of control than did values for total lipids or for phospholipids. In 1949, as part of a study of degenerative changes in a group of young diabetics in varying degrees of control,[6] single serum cholesterol values were obtained in this clinic that confirmed Butsch's work. The Iowa studies demonstrated also that, although mean cholesterol levels varied inversely with the degree of diabetic control, the value for a given patient might not conform to the general rule.

MATERIALS AND METHODS

Serial serum choleserol values were obtained in 48 cases of diabetes mellitus of recent onset, observed in this clinic in the past three years; 435 determinations form the basis of the study. The ages of the children at the time of onset of diabetes range from 4 months to 15 years. Insulin therapy was instituted the first month after onset for 73 per cent, between 1½ and 2 months for 15 per cent, between 3 and 7 months for 10 per cent, and it was not known for 2 per cent. The patients were observed for varying periods, ranging from 1 to 24 months. During the study period the number of

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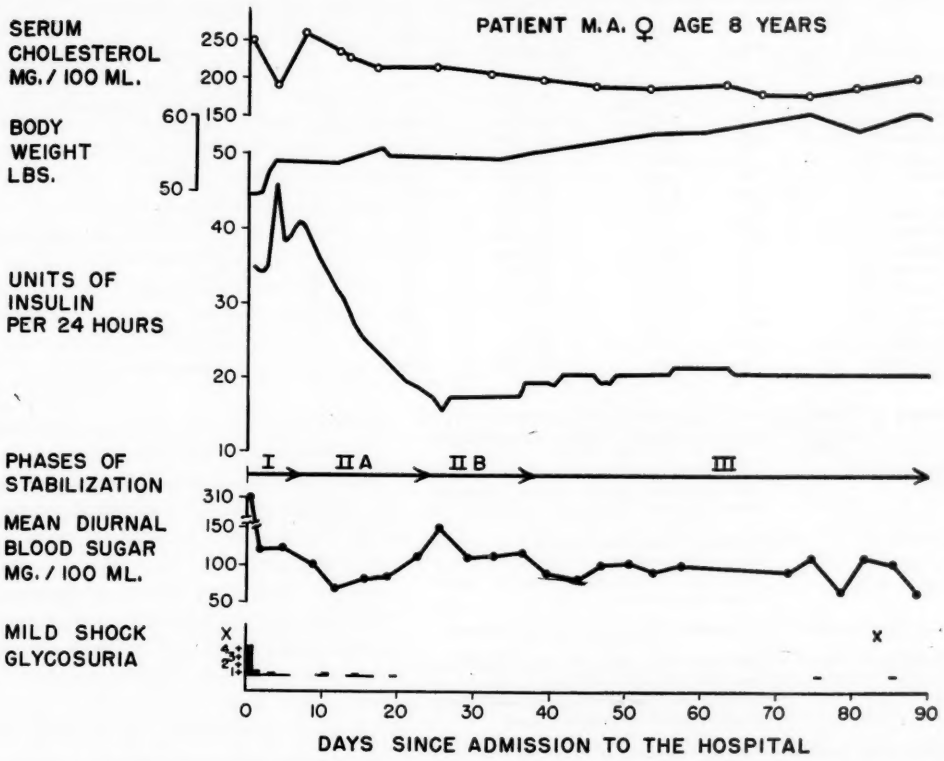

FIGURE 1 Typical response to treatment of a child with diabetes mellitus of recent onset. Mean diurnal blood sugars represent the average of seven serial blood sugar determinations during a 24 hour period. Degree of glycosuria represents the average qualitative value of the four daily fractional urine specimens. The phases of stabilization are defined in the text.

cholesterol determinations made for each case ranged from 3 to 26 with a median of 7.

An effort was made to obtain serum from the patient before and shortly after insulin therapy was begun and thereafter at weekly intervals throughout the period of hospital care. Blood samples were collected in the morning between breakfast and lunch. Rabinowitch[15] stressed the importance of fasting specimens, but the more recent studies of Turner,[35] of Boyd[36] and of Bruger and Somach[37] have demonstrated that no significant variation of the serum cholesterol level occurs during the day.

All urine excreted was collected and examined for sugar and ketone bodies. Diurnal blood sugar determinations (8 times per day) were made once or twice a week.

Graphic charts were made for each patient as shown in Figure 1. The cases were classified as to stage of disease and degree of control as defined in Table 2.

Disagreement exists in the literature regarding the normal range of serum cholesterol. The lack of agreement arises primarily from use of different chemical methods. The range of normal values obtained by various authors is shown in Table 1. The Bloor method[32] was used in this clinic until January, 1952 and Butsch, using this method, obtained a mean value of 188 mg. per 100 ml. with a standard deviation of ± 19 mg. per 100 ml. for 50 normal children.[18] In view of the advantages and greater acceptability of the Schoenheimer-Sperry method,[33] 186 duplicate determinations by the Bloor and Schoenheimer-Sperry methods of serum cholesterol of patients with different diseases were analyzed in our laboratory and a correlation coefficient of 0.97 was obtained for the paired values. For the purpose of this study the Bloor values obtained prior to January, 1952 were converted to comparable Schoenheimer-Sperry values by using a regression equation based on the correlation coefficient 0.97. In

TABLE 1 THE RANGE OF NORMAL SERUM CHOLESTEROL VALUES FOR CHILDREN AS OBTAINED BY DIFFERENT METHODS

AUTHOR	NO.	AGE	RANGE mg./100 ml.	MEAN mg./100 ml.	SD	METHOD	YEAR
Boyd (19)	29	newborn	17-86	34	15	Modified Bloor	1936
Sperry (20)	63	1-25 da.	71-190	133	25	Schoenheimer-Sperry	1936
Gyorgy (21)	13	2-13 yr.	144-250	185	—	Colorimetric	1926
Rabinowitch (15)	46	3-14	111-234	176	—	Bloor	1929
Acuna (22)	22	3-14	113-230	149	—	Colorimetric	1930
Ward (23)	49	6-13	125-158	136	—	Lieboff	1931
Kaiser (24)	29	5-16	108-201	150	22	Bloor	1934
Molitch (25)	213	8-15	81-204	131	—	Sackett-Reinhold	1936
Offenkrantz (26)	107	3-12	112-287	183	47	Modified Schoenheimer-Sperry	1936
Erickson (27)	16	5-9	109-235	182	—	Gasometric	1937
Hansen (28)	28	2-15	160-281	199	26	Bloor	1937
Radwin (29)	51	0-16	107-299	193	28	Colorimetric	1940
Butsch (18)	50	2-19	143-229	188	19	Bloor	1942
Hodges (30)	417	2-13	—	205	38	Schoenheimer-Sperry	1943
Thomas (31)	24	6-14	130-275	210	—	Bloor	1947
This study	44	2-16	127-268	204	34	Schoenheimer-Sperry	1952

TABLE 2 DEFINITION OF CONTROL OF DIABETES MELLITUS IN CHILDREN UNDER HOME MANAGEMENT

III—Excellent	Freedom from sugar in the urine except for occasional slight traces. Approximately normal blood sugar values.
IIB—Good	Freedom from sugar in the urine except for occasional traces and one plus, occasional mild shock. Approximately normal blood sugar values.
IIC—Good to fair	Fluctuating from good to fair control.
ID—Fair	Less than one half of urine specimens free from sugar and small amounts of sugar in the remaining specimens. Slightly elevated blood sugar values.
IC-ID—Fair to poor	Varying amounts of sugar in the urine continuously. Elevated blood sugar values. Fluctuation from ID to IC.
IC—Poor	Continuous gross glycosuria. Markedly elevated blood sugar values.

addition, duplicate serum cholesterol determinations were made by the Bloor and Schoenheimer-Sperry techniques on 44 normal children. The correlation coefficient obtained was 0.79, a lesser degree of correlation than was obtained on the series of 186 patients. The difference in correlation may be explained by the smaller number of determinations and by the narrower range of the values of the normal group. The mean cholesterol value of the normal subjects by the Schoenheimer-Sperry method was found to be 204 mg. per 100 ml. and the standard deviation 34 mg. per 100 ml. The mean and normal range were identical with the values obtained by Hodges, Sperry and Anderson[30] who studied 417 normal children of ages comparable to those in this study.

Duplicate serum cholesterol values also were determined in 73 cases of diabetes by the Schoenheimer-Sperry method in our laboratory and by the Kendall method[34] in the University of Pittsburgh laboratory. The correlation coefficient obtained was 0.93. The mean serum cholesterol value obtained for the 73 diabetic subjects using the Schoenheimer-Sperry method was 249 mg. per 100 ml. as compared to the mean value of 233 mg. per 100 ml. obtained using the Kendall method. Values for serum cholesterol determined in the University of Pittsburgh laboratory by the Kendall method have been found to be in close agreement with four other major research laboratories.

CLINICAL MANAGEMENT

Treatment pursued by the Pediatric Clinic is based on the premise that the diabetic child has a normal propensity for health as long as the disease is well controlled.[38, 39, 40] Insulin is administered on a percentage distribution basis. The diet contains approximately 20 to 35 calories per pound of body weight and 1.0 to 1.5 gm. of animal protein per pound of body weight.

When first admitted to the hospital the child is given enough insulin to control glycosuria. The period of time necessary to check glycosuria and hyperglycemia is called the stage of rapid clinical improvement (Stage I). The period of time during which the insulin requirement decreases gradually is called the stage of metabolic recovery (Stage IIA). Frequently, the insulin dose is decreased below the insulin requirement and minimal glycosuria recurs. This stage is called the transitional period (Stage IIB). The insulin dose is then raised to that level necessary to maintain aglycosuria and normoglycemia. The patient thus passes through a transitional period to the stage of excellent control of the disease (Stage III). Figure 1 depicts the above stages in a typical case.

The child is discharged from the hospital when con-

trol is established. Detailed instructions for home care are given to the child and parents. They are taught to keep a daily home record including entries for the results of the four urine examinations, the daily insulin requirement, the description of intercurrent infections and their treatment, the amount and variation of physical activity, the diet, and the trend of emotional patterns. The home records are presented for analysis at each subsequent out-clinic visit. As a rule, each patient is examined three or four times a year. The degree of control is established as defined in Table 2 on the basis of the home records and the results of blood and urine sugar analyses on the day of the examination. Serum cholesterol values are obtained the morning of each clinic visit.

RESULTS

Serum cholesterol at the beginning of treatment. Serum cholesterol values were obtained in 14 cases before the institution of insulin therapy and in 4 additional cases one day after insulin therapy was begun. In 13 of this group of 18 cases, there was ketosis at the time of admission; it was mild in 3 cases with normal values for carbon dioxide combining power, severe in 3 with low carbon dioxide values. Serum cholesterol values in the 13 cases ranged from 126 to 339, averaging 213 mg. per 100 ml. The mean serum cholesterol of the 3 patients with normal carbon dioxide combining power was 237; in those with low values, 226. In case D.B., in which the initial serum cholesterol was 980 mg., there was acetonuria upon admission, and intravenous therapy was required. In case L.C., in which the initial serum cholesterol was 1220, insulin had been used, though in inadequate amounts, and acetonuria was not demonstrated on admission. These observations reveal that hypercholesterolemia was not related to ketosis and acidosis in this group of cases.

In 5 cases, in which there was evidence of dehydration at the time of admission, there was a rapid increase in weight and decrease in the serum cholesterol value within the first days of insulin and fluid therapy. This is illustrated in Figure 1.

Serum cholesterol during phases of stabilization. The wide fluctuation in serial serum cholesterol values during the period of stabilization is shown in Figure 2. An initial decrease in the level of serum cholesterol is observed frequently during the first few days of therapy. Later, but early in therapy, the serum cholesterol tends to increase. As therapy continues, the cholesterol falls within the normal range or approaches the normal range.

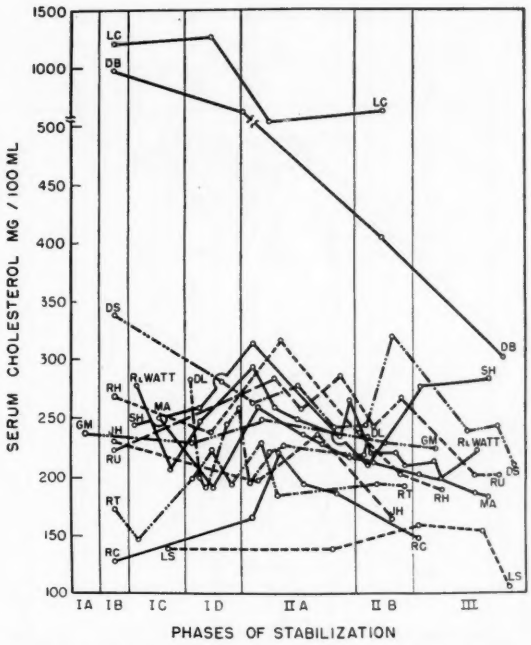

FIGURE 2 This chart demonstrates the marked fluctuations in serial serum cholesterol values concurrently with the improvement of the patient after institution of adequate therapy. The phases of stabilization are defined in the text.

Serum cholesterol during home treatment. In Figure 3, all the serum cholesterol values are grouped in time periods relative to the institution of insulin therapy. During the period of observation the cholesterol values are distributed over a wide range. It is remarkable that many low values are recorded. After the first ten days of therapy the mean serum cholesterol value increases. The mean value then decreases so that during the fourth month the lowest values are observed. Because of the large number of subnormal values the mean serum cholesterol after the second month of therapy is below the mean value for normal children. None of the patients had symptoms, signs or laboratory findings of hyperthyroidism, anemia or tuberculosis.

In 43 of the 48 cases, there was a typical response to therapy and excellent control was established at the time of discharge from the hospital. The other five patients were in only fair to good control during the period of stabilization. After discharge from the hospital, seven children sustained excellent control and 12 remained in good control throughout their periods of observation. The serial serum cholesterol values in individual cases in which determinations were made

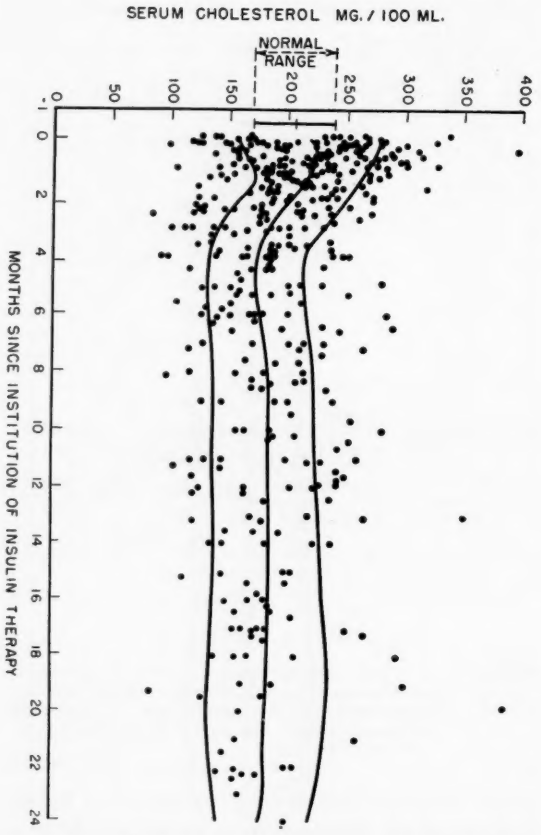

FIGURE 3 Distribution of all the serum cholesterol values according to months after institution of insulin therapy. The heavy lines represent the smoothed values of the mean and one standard deviation above and below the mean of all the values. The mean and one standard deviation above and below the mean of normal children is presented to the left of the graph.

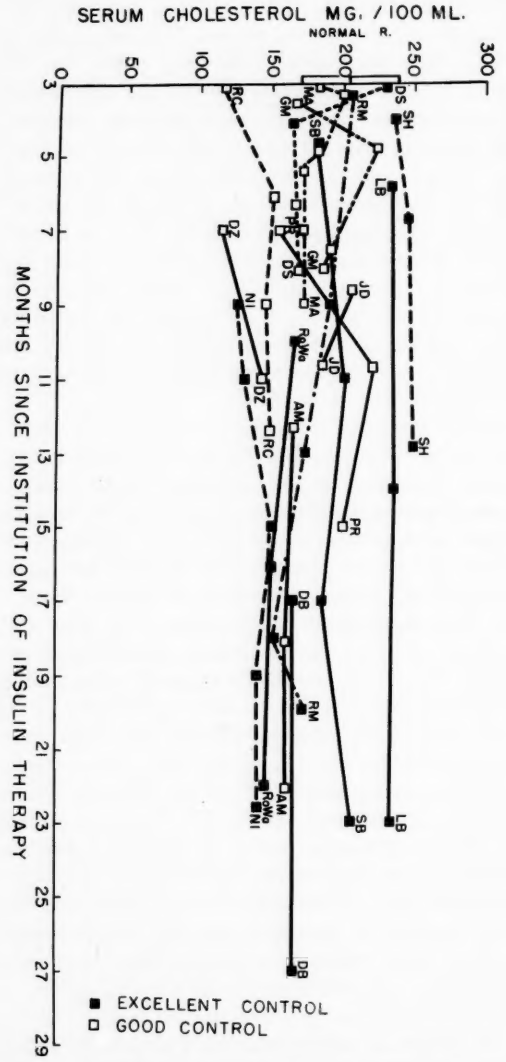

FIGURE 4 Serial serum cholesterol values of patients remaining in excellent and good diabetic control during the period of home management and after the third month of therapy. The symbol represents the degree of control at the time of and the interval prior to the observation of the serum cholesterol.

after the third month of therapy are charted in Figures 4, 5 and 6. The patients are grouped according to their degree of control during the greater part of the period of observation. With lessening of the degree of diabetic control, the amount and range of fluctuation of serum cholesterol values increase. Fluctuations of more than 50 mg. per 100 ml. are noted in only 3 of 14 cases in good to excellent control, in 14 of 23 cases in fair to good control, and in 8 of 10 cases in fair to poor control. In the last named group there were not only wider fluctuations; in two cases there were values over 300 mg. per 100 ml. for periods of two or more months. One patient, R.Sc., two years of age, in fair control, however, maintained a consistently low and relatively constant serum cholesterol over a period of 19 months. Patient J.H., 13 years of age, maintained cholesterol levels within the normal range for a period of 21 months despite periods of fair and poor control. These findings illustrate the fact that the general rule does not always hold for the individual patient. Serum cholesterol values of stabilized patients, for the most

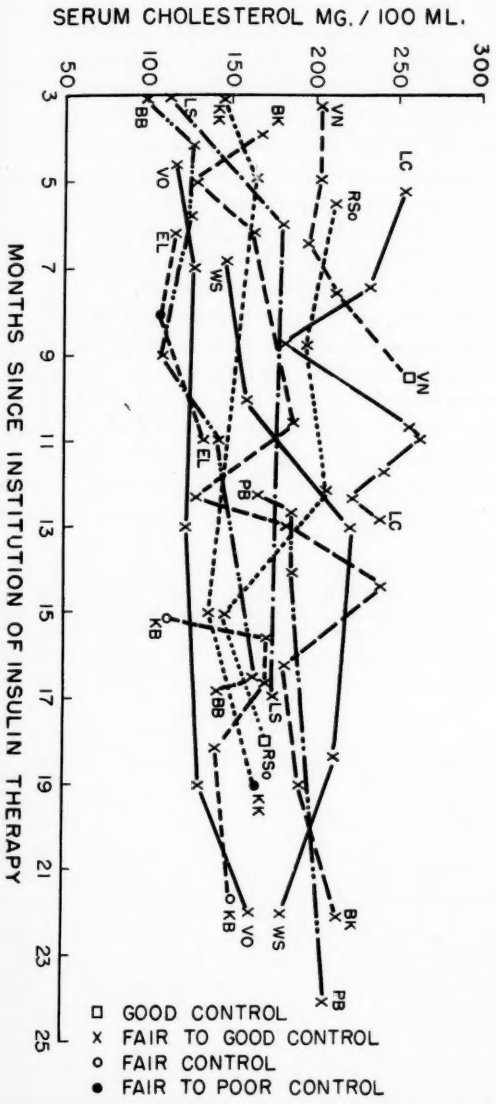

FIGURE 5 Serial serum cholesterol values of patients fluctuating from good to fair control during the period of observation.

part, remained in the normal range. Subnormal values were found in each of the four groups classified according to control.

In Figure 7 are shown changes observed in a case in which the serum cholesterol value was high at the time of admission, decreasing during the early months of treatment when the disease was in good control, but increasing to a very high level over a period of 11

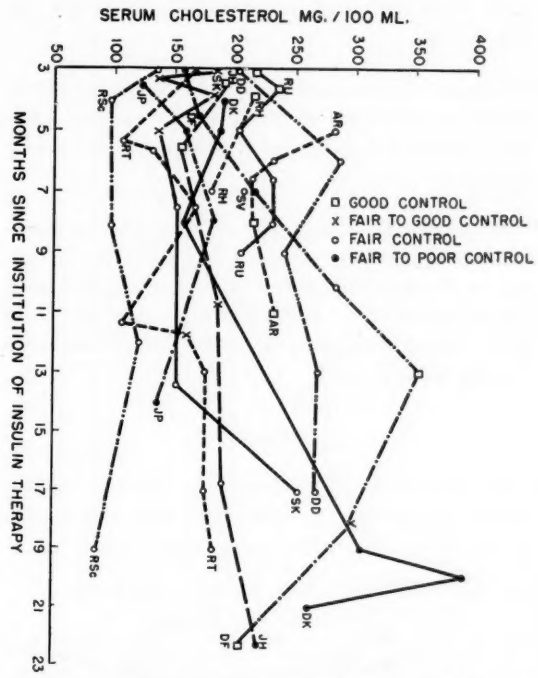

FIGURE 6 Serial serum cholesterol values of patients in fair to poor control or fluctuating degrees of control.

months at a time when the degree of control was only fair to poor. In the following period of fair to good control the serum cholesterol remained elevated for at least two months, but after eight months decreased to the upper limits of the normal range.

Extreme hypercholesterolemia. In two cases, the serum cholesterol was extremely high at the time of admission (Figure 8). One patient had had symptoms of diabetes mellitus for three weeks prior to admission to the hospital and had received no special fluid diet. She had acetonuria and required intravenous fluild therapy. The other patient had been a known diabetic for three months. She had been on a free diet with 20 units of protamine zinc insulin daily. The diabetes was poorly controlled at admission, although her urine was free of ketone bodies. Neither child exhibited lipemia retinalis or xanthoma diabeticorum. The serum cholesterol values decreased rapidly during stabilization. One patient continued to remain in excellent control after discharge from the hospital and her cholesterol value is now well within normal range. The other patient, whose home environment is very unstable, has maintained only fair control and her more recent choles-

terol values have fluctuated between 200 and 300 mg. per 100 ml.

Infection. In five cases there was a temporary fall in the serum cholesterol during or soon after acute infection (Figure 9). A significant change does not always occur.

Sex, age, insulin requirement and weight. The serum cholesterol value was apparently not related to the sex, age or insulin requirement in these 48 cases. Except where malnutrition or obesity were associated with poor control, there was no definite correlation with weight or body build.

COMMENT

The serum cholesterol values of 48 children observed shortly after onset of diabetes varied from 100 to 1220 mg. for each 100 ml. At least half the values obtained were within the range found for nondiabetic children. Of those outside this range, nearly as many values were below as above it. Concurrently with the correction of hyperglycemia, glycosuria and malnutrition by insulin and diet therapy, the serum cholesterol values of almost all patients increased for a short period of time. None of the patients had enlargement of the liver by physical examination and no liver biopsies were done. The cause of this relatively sudden elevation is not known but may reflect mobilization of lipid stores.

Keys and others[43] have reported serial serum cholesterol values for normal adult subjects. The younger individuals of their series showed less fluctuation in values than the older subjects. Concensus indicates that each normal individual tends to maintain his serum cholesterol level within a narrow range, but that the level varies widely in different individuals. Hunt and others[44] have pointed out that in adults values above

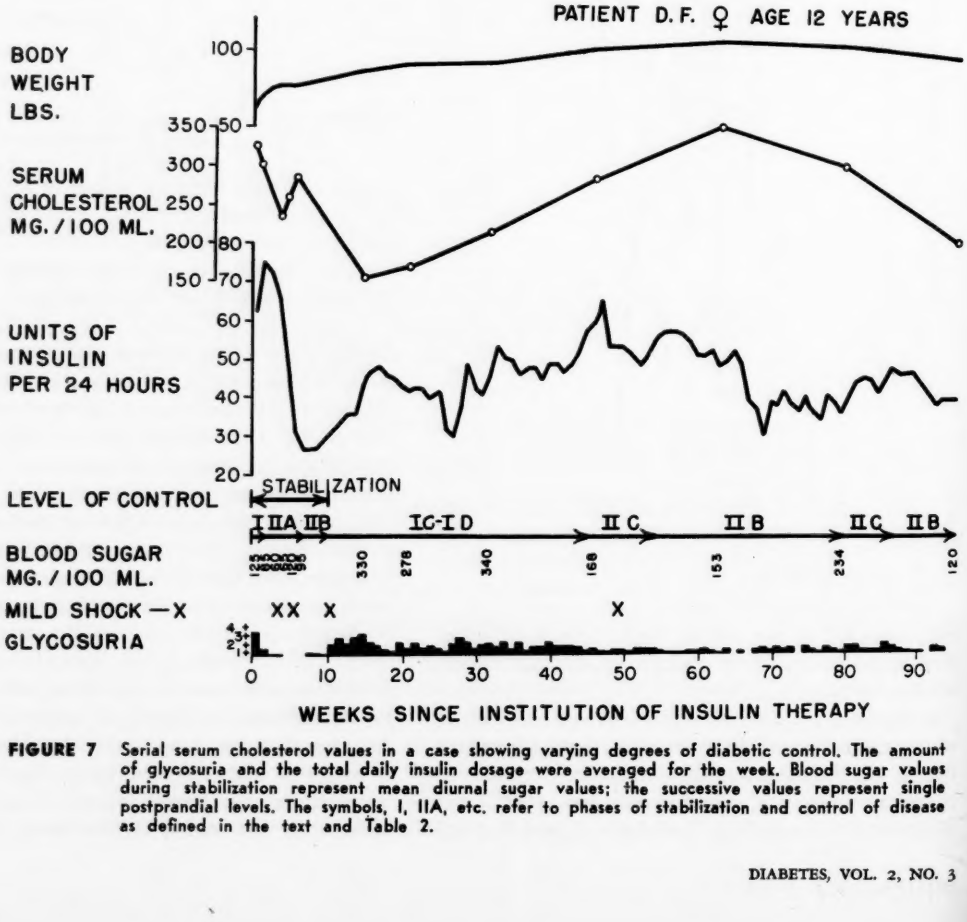

FIGURE 7 Serial serum cholesterol values in a case showing varying degrees of diabetic control. The amount of glycosuria and the total daily insulin dosage were averaged for the week. Blood sugar values during stabilization represent mean diurnal sugar values; the successive values represent single postprandial levels. The symbols, I, IIA, etc. refer to phases of stabilization and control of disease as defined in the text and Table 2.

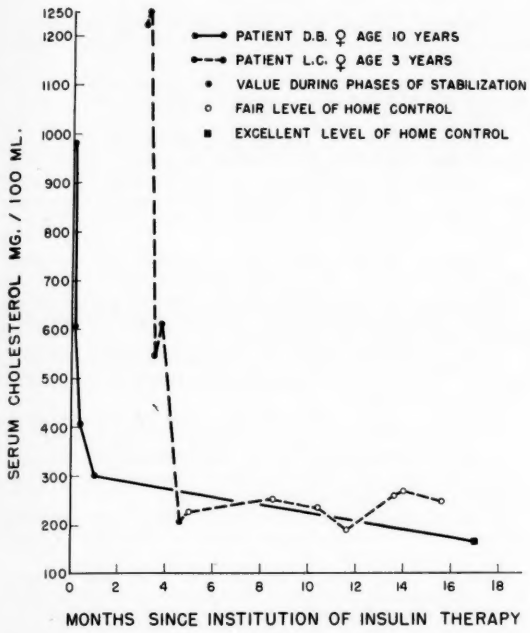

FIGURE 8 Serial serum cholesterol values in two cases showing extreme hypercholesterolemia.

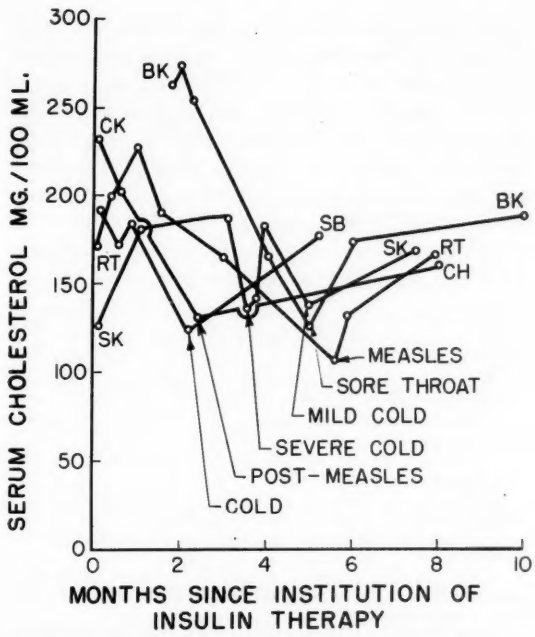

FIGURE 9 Changes in serum cholesterol values during and immediately after infection.

400 mg. and below 90 for each 100 ml. (Bloor's method) were of serious prognosis. The findings of this series of observations made during the first two years after onset show that the serum cholesterol values of diabetic children fluctuate markedly at the beginning of treatment, and thereafter only patients maintained in good control tend to sustain normal values.

After the period of initial regulation the level of serum cholesterol appears to change with degree of control of the disease not as an immediate response but as a result of weeks or months of a given degree of control. A single serum cholesterol value cannot be used as an accurate measure of degree of control, but an abnormal value usually reflects a previous period of inadequate control.

Lipotropic substances such as choline, inositol, methionine and betaine are advocated for diabetic patients with abnormal serum cholesterol values. This study indicates that the degree of control is a factor, as well as others, such as dehydration and infection, to consider in evaluating the efficacy of lipotropic agents in regulating lipid metabolism.

The belief is becoming more widely accepted that a high degree of diabetic control offers the best means of averting or delaying chronic degenerative changes.[7, 8, 10] We do not as yet know if the level of serum cholesterol is an index sufficiently sensitive to reflect alterations in lipid metabolism that are associated with atherosclerosis.[45] Only serial serum cholesterol values obtained on groups of patients in known degrees of diabetic control over a long period of time will permit accurate deductions regarding the interrelationships of level of serum cholesterol, degree of control and the development of vascular degenerative changes.

SUMMARY

In a study of 48 cases of juvenile diabetes early in its course, 435 determinations of serum cholesterol were made. The initial serum cholesterol values varied from 100 to 1220 mg. per 100 ml. The age, sex, diet prior to admission, duration of symptoms, presence or absence of acidosis or ketosis, the degree of malnutrition, or the insulin requirement failed to explain the wide variations observed. In 44 normal children, the mean serum cholesterol (by the Schoenheimer-Sperry method) was 204, the standard deviation 34 mg. per 100 ml.

After the period of initial regulation, the level of

serum cholesterol appeared to change with the degree of control of the disease, not as an immediate response but as a result of weeks or months of a given degree of control. Almost all patients who maintained excellent or good control had a relatively constant serum cholesterol level within the normal range. Patients who achieved only fair to poor control usually continued to show marked fluctuations in serum cholesterol values.

In 5 cases a severe or mild infection was accompanied by a significant decrease in serum cholesterol values.

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ABSTRACTS

Agatston, Howard J. *(Paper presented at the N. Y. Soc. for Clin. Ophthalmology)*: OPHTHALMOSCOPIC FINDINGS IN KIMMELSTIEL-WILSON SYNDROME. Am. J. Ophth. *35*:1827, December 1952.

The diagnosis of intercapillary glomerulosclerosis can be verified only by a postmortem renal examination, but it should be suspected in a long-standing case of mild diabetes with retinopathy and renal dysfunction.

Aikawa, Jerry K.; Felts, John H., Jr.; and Harrell, George T., Jr. *(North Carolina Babt. Hosp. and the Bowman Gray Sch. of Med. of Wake Forest Coll., Winston-Salem)*: ISOTOPIC STUDIES OF POTASSIUM METABOLISM IN DIABETES. J. Clin. Investigation *32*:115-21, January 1953.

The exchangeable potassium content (Ke) was determined by the radioactive isotopic technic in 42 unselected diabetic subjects. The initial Ke values were significantly lower in diabetic males than in normal male subjects. No significant difference was found in Ke between diabetic and normal female subjects. Seven of the 20 subjects in whom serial determinations were performed showed an increase in Ke of more than 20 per cent. In general, the control of the diabetes was poorer in these 7 subjects than in the 13 remaining individuals who did not show an increase in Ke. The results suggest that the presence or absence of a potassium deficit in diabetes can be correlated roughly with the relative adequacy of control of the disease.

Allen, Frederick M. *(New York Polyclinic Med. Sch. and Hosp.)*: CURRENT JUDGEMENTS ON METABOLIC CONTROL AND COMPLICATIONS IN DIABETES. New England J. Med. *248*:4133-36, January 22, 1953.

The author states that the blood sugar can nearly always be kept within normal range (not above 150 mg. per 100 cc. throughout twenty-four hours) without frequent hypoglycemic troubles and without spoiling the happiness of any sincerely co-operative patient (except for the rare "labile" patient). With this control, in addition to salt restriction when indicated, the author believes that complications are absolutely prevented or, when they exist, are generally arrested.

He suggests that the reward of diabetic patients for their strict care may be a lower incidence of premature degenerations than among the general population.

Barnard, Donald M.; Story, Robert D.; and Root, Howard F. *(Joslin Clin., New Eng. Deaconess Hosp., Boston)*: URINARY TRACT INFECTIONS IN DIABETIC WOMEN. New England J. Med. *248*:136-41, January 22, 1953.

Among 52 diabetic patients referred to a special clinic for urinary tract infections, 51 were women. This suggests that the cause was urethral contamination rather than blood-borne infection. The infecting bacteria were predominantly colon-dwelling organisms—a fact consistent with an urethral transmission of the infection. Prophylaxis should include the prompt and repeated instruction of all diabetic girls and women in the importance of perineal and rectal hygiene. Only 5 cases were cured and 29 improved by intensive use of antibiotics.

Bartelheimer, Heinrich *(Medizinischen Universitätsklinik Kiel)*: SIALOLITHIASIS IN DIABETICS. Deutsche medizinische Wochenschrift 77:936-38, August 1, 1952.

The occurrence of salivary calculi repeatedly observed in diabetics during a relatively short period of time is the occasion to point out that the changes occurring in the mouth cavity of diabetics further the formation of concretions. Other researchers should also be stimulated to investigate whether this combination really occurs frequently. Because they can lead to dangerous deterioration of the metabolism, it is recommended that salivary

calculi diagnosed in diabetics be removed. The x-ray examination is made easier by a simple and economic photographic technic (described in detail).

Beaudoin, Rachel; and Mayer, J. *(Harvard Sch. of Pub. Health, Boston)*: FOOD INTAKES OF OBESE AND NON-OBESE WOMEN. J. Am. Dietet. A. *29*:29-33, January 1953.

Unless special precautions are applied to the study of the fourth of the adult population which is overweight, any data collected on the caloric intake of populations by the record method is likely to be an underestimate. In contrast to various unsupported assumptions in articles published on the subject, it was found that the average caloric intake of obese women did not contain a significantly higher proportion of either carbohydrate or fat than did that of their normal weight controls.

Berner, Jørgen H., Jr., *(Med. Dept. A, Rikshospitalet, Oslo)*: ORTHOSTATIC HYPOTENSION IN DIABETES MELLITUS. Acta medica scandinavica *CXLIII*:336-40, August 5, 1952.

Postural hypotension was demonstrated in 7 patients with long-standing diabetes. All of them showed signs of neuropathy, with one or more signs indicative of involvement of the autonomic nervous system.

Bleehen, N. M.; and Fisher, R. B. *(Dept. of Bio-chemistry, Univ, of Oxford)*: THE ACTION OF INSULIN ON THE SURVIVING RAT'S HEART. J. Physiol. *118*:27P-28P, October 28, 1952 (Abstract of paper presented at the meeting of the Physiological Society, Physiological Department, University New Buildings, Edinburgh, July 4-5, 1952).

Provided that the Ringer's Solution is very thoroughly filtered, closed-circuit perfusion of the surviving rat heart at coronary flow rates of 4 to 8 ml./min. can be maintained for at least 2 hours without the occurrence of appreciable edema. When the surviving heart is perfused with medium containing 150 mg./100 ml. of glucose and 0.2 mU insulin per ml. for 15 minutes and then switched to similar medium without insulin, the glucose utilization in the period beginning 15 minutes after the change-over is no greater than on initially insulin-free medium. This finding suggests that the "chemical combination" of insulin with muscle postulated by Stadie, Haugaard, March, and Hills (1949) may be an artifact.

Bottger, H.; Romer, K.; and Seitz, R. EFFECT OF ALLOXAN ON AN ISLET TUMOR OF THE PANCREAS. Klinische Wochenschrift 30:507-10, June 1, 1952.

Alloxan was given to a patient who had an adenoma of the islet cells of the pancreas but who rejected surgical treatment. The frequency and the severity of attacks of hypoglycemia were not influenced. Death without relation to the alloxan treatment occurred in one of the many attacks of hypoglycemic coma. The histological structure of the pancreatic adenoma gave no indication that the alloxan had had a damaging effect.

Five previous reports of alloxan treatment of human patients are reviewed, with the conclusion that surgical removal is the only effective treatment of islet tumor.

Brewster, William R., Jr.; Bunker, John P.; and Beecher, Henry K. *(Anesthesia Lab. of Harvard Med. Sch. at the Mass. Genl. Hosp., Boston, Mass.)*: METABOLIC EFFECTS OF ANESTHESIA. VI. MECHANISM OF METABOLIC ACIDOSIS AND HYPERGLYCEMIA DURING ETHER ANESTHESIA IN THE DOG. Am. J. Physiol. *171*:37-47, October 1952.

Twelve dogs anesthetized with ether to arterial levels of 90 mg. per 100 cc. after a total epidural preganglionic sympathetic block showed no alteration in lactic acid, pyruvic acid, lactic acid/pyruvic acid ratio, total fixed acids, serum potassium, or blood sugar during the period of anesthesia. Five dogs with total sympathetic block, with arterial ether levels of 100 to 180 mg. per 100 cc. (sufficient to reduce cardiac output and peripheral blood flow), showed no change in blood sugar or pyruvic acid but did exhibit consistent rises in lactic acid, total fixed acids, and serum potassium.

These changes were small in magnitude as compared with those observed in the unblocked ether-anesthetized dog and probably resulted from tissue anoxia, with a consequent anaerobic glycosis and lactic acid formation in cellular carbohydrate metabolism. The metabolic acidosis with rise in lactic and pyruvic acid, the hyperglycemia, and the fall in serum potassium, which occur during ether anesthesia in the dog, are directly related to the quantitative output of epinephrine. Total epidural preganglionic sympathetic block prevents this reflex sympatho-adrenal output of epinephrine and nor-epinephrine in the dog during ether anesthesia.

Bruch, Ernest *(St. Anthony Hosp., Rockford, Ill.)*: PROGRESS IN INSULIN PHYSIOLOGY. Journal-Lancet 72:516-17, November 1952.

A brief review is given of the important contributions to the study of carbohydrate metabolism and insulin therapy.

Cascio, G. HEMATOLOGICAL AND METABOLICAL ASPECTS OF PATIENTS WITH THROMBOSIS OF THE CENTRAL RETINAL VEIN. Annales d'oculistique *185*:640-51, July 1952.

Among 13 cases of thrombosis of the central vein of the retina, only 4 individuals were free from hypertension, arteriosclerosis, or diabetes; two of the 13 were diabetic. There was increase in prothrombin time in 5 cases; and an increased blood cholesterol level in 4 cases.

Conn, Jerome W.; Fajans, Stefan S.; Louis, Lawrence H.; and Seltzer, Holebrook S. *(Ann Arbor, Mich.)*: A METABOLIC EVALUATION OF THE RABEN-WESTERMEYER GROWTH HORMONE IN A PITUITARY DWARF WITH COEXISTING DIABETES MELLITUS. J. Lab. & Clin. Med. *40*:788, November 1952.

A fraction of hog pituitary known to produce growth in animals was prepared by Raben and associates and given intramuscularly to a 17-year-old boy with panhypopituitarism due to a calcified craniopharyngioma plus the very rare coexistence of diabetes mellitus. The results of a detailed metabolic balance study over a 24-day period were as follows: (a) Significant anabolism of body protein was produced in this human being with the Raben-Westermeyer growth preparation; (b) no intensification of the diabetic state was observed; (c) the anabolic effect of growth hormone was not intensified by administration of insulin; (d) insulin alone was definitely protein anabolic in this diabetic pituitary dwarf who without insulin maintained nitrogen equilibrium. Hence, this preparation induced growth in a human pituitary dwarf without affecting carbohydrate metabolism.

Cordes, Frederick C. *(Dept. of Ophthalmology, Univ. of California Sch. of Med., San Francisco)*: THE DIABETIC: HIS VISUAL PROGNOSIS: THE THIRD JOHN E. WEEKS LECTURE. A.M.A. Arch. Ophth. *48*:531-56, November 1952.

On the basis of personal experience and a review of the literature, the author draws the following conclusions regarding the visual prognosis for the diabetic patient: (1) The visual prognosis of rubeosis iridis is poor; (2) Extraction of a true diabetic cataract or of a senile cataract in a diabetic patient offers a good prognosis for vision, provided there is no retinopathy. It is important that all foci of infection be cleared up before operation, that the diabetes be controlled in the hospital for several days before operation, and that insulin not be given in large amounts on the day of operation; (3) The young diabetic who survives twenty years is very likely to have a severe form of diabetic retinopathy with loss of vision, irrespective of the level of control at which the disease has been maintained; (4) Since the disease in the adult occurs as a rule between the ages of forty and seventy years, only about 40 per cent of patients with diabetes acquired in adult life have retinopathy; (5) The adult diabetic who survives twenty years with the disease will almost certainly have retinopathy, but the retinal process will usually progress more slowly than it does in the juvenile diabetic; (6) Although almost all observers have agreed that the treatment of diabetes has no effect on the development of retinopathy, recent scattered reports indicate that if present-day methods of control are carried out meticulously, the prognosis in the future may not be as black as it is now generally believed to be; (7) In view of the devastating effect of loss of vision, the physician managing a diabetic patient carries a grave responsibility of leaving no stone unturned to assure the best possible control of the diabetes and, thus, perhaps prevent visual loss. To this end, he should take full advantage of the accumulated knowledge available to him.

Cornforth, J. W.; and Long, D. A. *(Nat. Inst. for Med. Res., Mill Hill, London)*: INFLUENCE OF CARBOHYDRATE METABOLISM ON BACTERIAL ALLERGY: ITS RELATION TO CORTISONE DESENSITIZATION. Lancet *1*:160-64, January 24, 1953.

Using the response to intradermal tuberculin as a measure of allergic hypersensitivity in albino guinea pigs injected with BCG, the authors find: (1) Single subcutaneous injections of adenosine diphosphate diminish sensitivity. This desensitizing action is first diminished and then abolished by the simultaneous injection of increasing amounts of adenosine triphosphate (ATP); (2) Single subcutaneous injections of ATP prevent desensitization by alloxan, cortisone acetate, and dehydroascor-

bic acid. They do not influence desensitization by glucose-l-phosphate; (3) Single subcutaneous injections of ATP not only abolish desensitization by cortisone acetate but actually increase hypersensitivity; (4) Single subcutaneous injections of insulin do not in themselves significantly influence sensitivity. The compensatory phase that succeeds insulin hypoglycemia is associated with desensitization; (5) The desensitization that succeeds insulin hypoglycemia is thought to be due to naturally liberated cortisone, since it does not occur in ascorbic-acid-deficient animals, is prevented by injection of reduced glutathione, and is intensified by injection of ATP; (6) Single subcutaneous injections of insulin prevent desensitization by alloxan and dehydroascorbic acid; they not only prevent desensitization but intensify sensitivity in animals treated with cortisone acetate; and they are without effect on the desensitizing action of glucose-l-phosphate; (7) Single injections of growth hormone depress sensitivity to tuberculin. This action was unaffected under the authors' experimental conditions by injection of reduced glutathione, ATP, or insulin or by ascorbic-acid deficiency; (8) In desensitization, growth hormone (given in single subcutaneous injections) has a synergistic action with either cortisone acetate or alloxan. The significance of these results is briefly discussed.

Creeth, J. M. (*Courtauld Inst. of Bio-chemistry, Middlesex Hosp. Med. Sch., London, England*): SEDIMENTATION AND DIFFUSION STUDIES ON INSULIN: THE MAXIMUM MOLECULAR WEIGHT. Biochem. J. *53*: 41-47, January 1953.

The sedimentation and diffusion characteristics of solutions of crystalline insulin have been investigated in the *p*H range 7-8; the variation of diffusion coefficient with concentration and *p*H confirms the evidence of dissociation advanced from other studies. Temperature change, within the range 14-30°, has no apparent effect on the dissociation equilibrium. The substance is apparently stable in the range *p*H 7.0-7.4 and at concentrations greater than 0.3 g./100 ml. Under these conditions, the sedimentation constant is 3.12 and the diffusion coefficient about 8.2. These values differ from previously accepted values. The diffusion and sedimentation results have been combined to give a maximum molecular weight of about 36,000 for this protein, in agreement with X-ray data on the solid substance.

Darrow, Daniel C.; and Pratt, Edward L. (*New Haven, Conn.*): RETENTION OF WATER AND ELECTROLYTE DURING RECOVERY IN A PATIENT WITH DIABETIC ACIDOSIS. J. Pediat. *41*:688-96, December 1952.

The retentions during recovery in a patient with severe diabetic acidosis were 114 gm. of water, 9 mEq of chloride, 13 mEq of sodium, and 6 mEq of potassium per kilogram of body weight.

In the light of this and previous studies, the significance of losses of water and electrolytes was discussed. It is pointed out that the acidosis is due in large part to accumulation of organic acids and that the loss of sodium in relation to chloride is little, if any, in excess of their ratio in extracellular fluids. The magnitude of the deficits of sodium, chloride, and water indicates that about 80 cc. per kg. of a fluid containing sodium and chloride in the ratio found in extracellular fluids suffice to replace most of the deficits of water and all the deficits of sodium and chloride. As long as all fluids are given parenterally, provision for water without electrolyte in glucose solutions must be given to cover the obligatory expenditure of water in urine and as insensible loss. Although potassium deficits are moderate, the effects of insulin are likely to produce a rapid and dangerous decrease in serum potassium concentration. Potassium should therefore be administered as soon as insulin begins to reduce blood sugar (in two to six hours). The amount to be given is apparently 2 to 4 mEq per kilogram during the first 24 hours.

Davidson, Sidney (*Lake Worth, Fla.*): DIABETIC NEUROPATHY. J. Florida M.A. *39*:500-04, January 1953.

The readiness with which more recent neuropathic lesions resolve and the stubbornness of those lesions which have lasted for some time are noteworthy. Based on the duration and the resistance to therapy of the lesions of diabetic neuropathy, a distinction in classification has been made, and it has been suggested that the pathologic physiology of the more recent lesions differs from that of the lesions of longer duration. The first type of neuropathy is a result of uncontrolled diabetes. If the uncontrolled phase has existed too long, the lesion may become irreversible. Hope should never be lost, however, since recovery has been known to occur years after starting therapy. Diabetic neuropathy is one of the early complications that cause pain. For this reason, it frequently leads to the discovery of the diabetes. In 2 cases, the uncomfortable neuropathy led to the dis-

covery of the uncontrolled diabetic state. Uncontrolled diabetes often does not cause enough discomfort and may go on for some time in the careless or unheeding patient without leading to adequate medical attention. Diabetic neuritis is the one complication that really hurts.

Davis, J. C. *(Dept. of Pathology, Univ. of Liverpool, Liverpool)*: HYDROPIC DEGENERATION OF THE ALPHA CELLS OF THE PANCREATIC ISLETS PRODUCED BY SYNTHALIN A. J. Path. & Bact. *64*:575-84, July 1952.

Synthalin A causes a gross hydropic degeneration of the alpha cells of the rabbit pancreas. The mechanism of this effect is not clear. Sodium diethyldithiocarbamate was found to cause histologic changes in the islets of rabbits, but specific necrosis of alpha cells was not seen.

Drucker, William R.; Miller, Max; Abbott, William E.; Craig, James W.; Jefferies, William McK.; Levey, Stanley; and Woodward, Hiram, Jr. *(Cleveland, Ohio)*: THE EFFECT OF STRESS ON GLUCOSE AND FRUCTOSE METABOLISM. J. Lab. & Clin. Med. *40*:794, November 1952.

The stresses of an acute febrile illness and surgery were studied relative to glucose and fructose tolerance. Five patients were given intravenous glucose and fructose tolerance tests on separate occasions before and after surgery. Thirty-five patients with typhoid fever were studied during the acute illness and convalescence, 34 for glucose tolerance and one for tolerance to both glucose and fructose. The results of these studies indicate that the tolerance for glucose as estimated by the blood sugar curve, hexose excretion, changes in pyruvic acid, and phosphorus is diminished by the stress of surgery or an acute febrile illness (typhoid). The tolerance for fructose, however, was unaltered in the surgical patients and in the typhoid case studied.

Duncan, Garfield G. *(Philadelphia)*: DIABETIC COMA—A THERAPEUTIC PROBLEM. Ann. Int. Med. *37*:1188-96, December 1952.

Stress is placed on the importance of the degree of ketonemia as an indication of the gravity of coma and as an indicator for the amount of the initial doses of insulin. Methods dealing with insulin therapy, hydration, and electrolyte, glucose, and alkali therapy, as employed at the Pennsylvania Hospital, are presented.

Dury, Abraham *(Dorn Lab. for Med. Research, Bradford Hosp., Bradford, Pa.)*: EFFECT OF INTRAVENOUS GLUCOSE ON TISSUE WATER AND IONIC CONTENT AND MODERATION OF POTASSIUM PLETHORA WITH EPINEPHRINE AND INSULIN PRETREATMENT. Am. J. Physiol. *171*:630-35, December 1952.

In experiments designed to study the mechanism of the similar effect of insulin and epinephrine upon the plasma potassium level, the water and ionic content of plasma, skeletal muscle, and liver after intravenous administration of a standard glucose dose was determined in groups of intact and of adrenalectomized-alloxan injected rats without other treatment and after epinephrine or insulin pretreatment in the latter animal preparations.

No significant changes in potassium or sodium content of the tissues of intact rats were found at 30 and 60 minutes after an infusion of a glucose solution. Administration of a similar quantity of glucose in adrenalectomized-alloxanized groups resulted in potassium plethora of plasma and muscle determined 60 and 90 minutes after glucose infusion associated with hyperglycemia. Both epinephrine and insulin pretreatment prevented the elevation in plasma potassium level. However, between the groups which were epinephrine- and insulin-pretreated, there were significant differences determined in ionic content of muscle and liver. The epinephrine-pretreated group exhibited an increased potassium content in muscle and liver not shown by the insulin pretreated group. The results indicated that different mechanisms were probably responsible for the apparently common effect of each humoral agent upon the plasma potassium level. The effect of insulin was probably associated with carbohydrate assimilation and utilization, whereas epinephrine apparently "blocked" potassium in muscle and liver in a manner not clear from the present data.

Editorial. *(Chicago, Ill.)*: GROWTH HORMONE AND CARBOHYDRATE METABOLISM. J.A.M.A. *150*:1602-03, December 20, 1952.

The importance of the islands of Langerhans, the adrenal medulla, the adrenal cortex, and the thyroid in carbohydrate metabolism are well recognized. Recent work has shown that still another endocrine factor must be added to the above list. It is an anterior pituitary factor other than corticotropin and most probably a growth hormone or some other hormone closely linked with it. In experimental studies, growth hormone pro-

duced diabetes in every case. It is possible that this diabetogenic action of growth hormone represents an exaggeration of a truly physiological blood-sugar-raising and anti-insulin action of the hormone in normal carbohydrate metabolism.

As to the mechanism of action of growth hormone in carbohydrate metabolism, it would seem that growth hormone does not enhance the new formation of sugar. Furthermore, it has not been shown that growth hormone facilitates glycogenolysis; its action is to inhibit the peripheral utilization of carbohydrate.

Editorial (*Trenton, N. J.*): HEPATIC HYPOGLYCEMIA. J. M. Soc. New Jersey 50:43, February 1953.

The mechanism of hepatic hypoglycemia is not clear, but may be related to the inability of the liver to store glycogen, or to break glycogen down to glucose, or to produce glucose from noncarbohydrate precursors. Many of the cases described had clearly evident clinical manifestations of liver damage, but a few most prominently showed the symptoms of hypoglycemia and first suggested the presence of significant liver disease. Hypoglycemia of hepatic origin may appear episodically, or be fairly constant. In mild form it produces nervousness, increased sweating, or palpitations, but in more severe states it may lead to bizarre, psychotic behavior, convulsions, shock, or coma. No definite relation could be found between the degree of clinically detected liver damage and the blood sugar level.

Editorials and Comments (*Chicago, Ill.*): GLYCOGEN STORAGE DISEASE. J.A.M.A. *151*:560, February 14, 1953.

In Gierke's disease there is usually an excessive deposition of glycogen in the liver and other affected organs. In spite of increasd amounts of carbohydrate in the liver, persons with the disease do not appear to be able to mobilize glycogen readily, as indicated by hypoglycemia during fasting, increased insulin sensitivity, and little elevation in blood sugar administration of epinephrine. It appears that at least one important factor in glycogen production is a definite enzymatic deficiency, a lack of glucose-6-phosphatase.

Ellis, Alexander *(Camden, N. J.)*: PREGNANCY AND DIABETES. J. M. Soc. New Jersey *49*:392-95, September 1952.

Rigid control of the diabetes is the most important single factor in the management of the pregnant diabetic. Ever since the discovery of methods of measuring pregnanediol excretion in the urine, attempts have been made to treat patients with hormones—chiefly estrogens and progesterone. Good infant survival rates have been reported with and without the use of hormones. There is no unanimity of opinion as to the method of delivery. At Cooper Hospital, the obstetricians believe that the contraindications to vaginal delivery are the same as in the nondiabetic: disproportion between the size of the fetal head and the pelvis, threatened eclampsia, etc. During the day of labor or induction, the dose of insulin in the mother is reduced considerably. This is to prevent the hypoglycemia that may take place immediately after delivery. There is a sudden fall in the blood sugar at this time. If the patient has been taking doses up to 25 or 30 units daily, the insulin is omitted entirely for the day. In the more severe cases, half the usual dose is given. The diet is "light" or "soft" and contains the usual amount of calories.

Elvehjem, C. A. (*Univ. of Wisconsin*): THE LIPOTROPIC ACTION OF PROTEINS. Science *116*:521, November 14, 1952.

The author reports that the lipotropic action of choline in preventing hepatic fat deposition is supplemented by the addition of casein or gelatin.

Engelberg, Hyman; Gofman, John; and Jones, Hardin *(Cedars of Lebanon Hosp., Los Angeles, and Univ. of California, Berkeley)*: SERUM LIPIDS AND LIPOPROTEINS IN DIABETIC GLOMERULOSCLEROSIS. Metabolism *1*:300-06, July 1952.

The blood lipids and lipoproteins were anlyzed in 14 patients with typical diabetic glomerulosclerosis. The serum cholesterol level was elevated in 11 patients and the phospholipid level in 10. The most striking finding was the marked elevation of the S_f 12-20 class of lipoproteins in the entire group of patients out of proportion to the elevation of the cholesterol level. It is suggested that the lipid metabolic defect, manifesting itself predominantly by a marked elevation in the S_f 12-20 class of lipoproteins, deserves evaluation both because it may have a causal relationship to the kidney lesion and because it may be an early finding in this disease. The use of heparin, both with and without fat restriction in the diet, is being investigated.

Engelberg, Hyman; and Massell, Theodore B. (*Los Angeles, Calif.*): HEPARIN IN THE TREATMENT OF ADVANCED PERIPERHAL ATHEROSCLEROSIS. A PRELIMINARY REPORT. Am. J. M. Sc. *225*:14-19, January 1953.

The authors present a preliminary report upon the treatment of peripheral atherosclerosis in 14 patients by the intravenous administration of 100 mg. of heparin 2 or 3 times weekly for a period of 6 months. No patient selected for this study had a palpable arterial pulse at either the popliteal or ankle level; all had markedly reduced oscillometric indices below the knee.

There was significantly improved digital blood flow in 8 of 14 extremities as determined by plethysmography. In 10 cases in which level walking tolerance could be determined, 8 showed marked improvement. Improvement occurred as a rule after 1 or 2 months of therapy. The reason for this favorable heparin effect is not known; the authors present several possible mechanisms of action.

Everett, W. G. (*Depts. of Ophthalmology and Pediat., Univ. of Pittsburgh Sch. of Med. and Children's Hosp., Pittsburgh*): NONDIABETIC LIPEMIA RETINALIS: REPORT OF A CASE. A.M.A. Arch. Ophth. *48*:713-15, December 1952.

A case of nondiabetic lipemia retinalis in a patient whose diet was high in fat is reported. The high-fat content was shown to play a part in the production of persistent lipemia retinalis as long as the diet was followed. The lipemia retinalis was seen to disappear in this patient after twenty-four hours of starvation. Such a diet may cause lipemia retinalis in some persons.

Foà, Piero P.; Santamaria, Leonida; Weinstein, Harriet R.; Berger, Sheldon; and Smith, Jay A. (*Dept. of Physiol. and Pharmacol., The Chicago Med. Sch., Chicago, Ill.*): SECRETION OF THE HYPERGLYCEMIC-GLYCOGENOLYTIC FACTOR IN NORMAL DOGS. Am. J. Physiol. *171*:32-35, October 1952.

The authors report 13 cross-circulation experiments upon dogs which support the hypothesis that the hyperglycemia-glycogenolytic factor is a second pancreatic hormone and that its secretion like that of insulin is regulated by the blood sugar concentration.

Friedenwald, Jonas, S. (*Wilmer Ophthalmological Inst. and Johns Hopkins Hosp.*): DIABETIC RETINOPATHY. J.A.M.A. *150*:969-71, November 8, 1952.

In typical cases of diabetic retinopathy visualization of the whole retinal vascular tree by special staining and injection technics, reveals enormous numbers of minute saccular aneurysms. Many of the aneurysms are thin walled; in others the walls are thickened and hyalinized. Sometimes the thickening of the walls almost obliterates the lumen. After the aneurysons are surrounded by clusters of hemorrhages and exudates, indicating that they are associated with or develop at points of weakness in the vessel wall.

Retinal capillary aneurysons are seen, not only in diabetics but in a variety of retinal diseases and even in some supposedly normal eyes. The characteristic features of the aneurysons of the diabetic are their great number, their sacular form, and their presence in uninjured portions of the retina. Here they must represent a primary vascular lesion in the retina, while in other diseases they occur in response to local injury.

There is an extremely close connection between this retinal vascular lesion of the diabetic and the renal lesion first described by Kimmelstiel and Wilson. The two lesions, when present, are almost jointly present and are joint manifestations of the same disease process.

The characteristic vascular lesions of the diabetic can occur in the absence of local or generalized atherosclerosis and in the absence of malignant hypertension and of its accompanying arteriolar lesions. It can also be said unequivocally that neither these retinal nor these renal lesions are regularly and characteristically seen in nondiabetics with atherosclerosis or malignant hypertension. The diabetic is susceptible to both atherosclerosis and hypertension; however, the characteristic retinal and vascular lesions of the diabetic cannot be attributed to atherosclerosis or hypertensive disease, although both these conditions may complicate the retinal and renal findings.

Hanum, in 1939, showed that patients with diabetic retinopathy often showed increased capillary fragility on the tourniquet test. This finding, confirmed by many subsequent observers, remains today the best evidence that the retinal and renal lesions are joint manifestations of a general capillary abnormality in these patients.

Lesions remarkably similar to the Kimmelstiel nodules can be produced in rabbits by the intramuscular injection of 7.5 mg. of cortisone daily for two weeks. More recently, Rich found typical Kimmelstiel lesions in the kidneys of a nondiabetic patient who had had long and intensive treatment with corticotropin (ACTH). These observations raise the question of whether adrenal

cortical function plays a role in the production of the capillary lesions of the diabetic.

Futcher, P. H.; and Long, N. W., Jr. (*Baltimore, Maryland*): OBESITY AND IMPAIRED CARBOHYDRATE METABOLISM IN THE "PREDIABETIC" MOTHERS OF LARGE INFANTS. J. Lab. & Clin. Med. 40:801, November 1952.

Women destined eventually to develop diabetes frequently are obese and often bear infants of excessive weight. In order to elucidate the part played by maternal obesity in the pathogenesis of these large infants, the records were studied of 12 pregnancies which occured in 10 women who weighed over 190 pounds in the third trimester and who were first recognized as suffering from diabetes six to twenty-two years later. The average weight of the 12 infants was 4,373 gm., significantly greater than the weight of infants born to two control groups of obese women. Glucose tolerance tests performed on two other "prediabetic" mothers during their childbearing era revealed impairment of carbohydrate metabolism, which preceded the recognition of frank diabetes by many years.

Gibson, John M. (*Montgomery, Ala.*): LIVING WITH DIABETES. J. M. A. Alabama 22:248-50, March 1953.

The person who finds he has diabetes needs to realize that he has to make necessary adjustments to the disease, and he must remember that they are permanent adjustments. But he need not regard himself as an invalid. Let him use reasonable care and plenty of good sense.

Givner, Isadore *(Chmn. of the Res. Comm. of the N.Y. Soc. for Clin. Ophth.)*: A GROUP STUDY OF DIABETES AND THE EYE. Am. J. Ophth. 35:1454-58, October 1952.

Ophthalmologists frequently discover early diabetes by changes in refraction. These discoveries are dependent upon changes in the index of refraction of the crystalline lens initiated by changes in the sodium chloride content of the aqueous humor and in the osmotic interplay following blood sugar shifts. In searching for causes of a retrobulbar neuritis or for an explanation of frequent lid infections, glycosuria is uncovered. Routine blood sugar tests made in every cataract case uncovers other cases of diabetes, even though (in the author's experience) cataract in the diabetic is no more common than in the nondiabetic. The finding of pin-point hemorrhages and exudates with normal retinal vessels usually means the presence of diabetic retinopathy. In this study, the number of females having diabetic retinopathy was twice that of the males. This sex distribution suggested to Saskin and his co-workers the possibility that the male hormone may favorably influence the pathologic process in the retina. The onset of retinopathy is influenced by the duration of the disease. Recently, the lipotropic factor of the pancreas has been singled out as important in the development of diabetic retinopathy. Renard and Dhermay emphasized the lipoidal character of the degenerative changes in the vessel wall and the high cholesterol blood level in diabetes with retinopathy.

Haunz, E. A. *(Grand Forks, N. Dak.)*: SUCCESSFUL MANAGEMENT OF THE DIABETIC PATIENT. Journal-Lancet 72:461-69, October 1952.

An attempt has been made to review some current therapeutic concepts of diabetes mellitus and certain basic principles of management of the disease in its uncomplicated form.

Haynes, Robert; Savard, Kenneth; and Dorfman, Ralph I. (*Worcester Foundation for Experimental Biol., Shrewsbury, and The Dept. of Biological Chem., Harvard Med. Sch., Boston, Mass.*): [illegible] OF ACTH ON ADRENAL SLICES. Science 116:[illegible] December 19, 1952.

The authors report that the output of corticosteroids by beef or pork adrenals was substantially enhanced by the action of ACTH.

Heck, W. *(Universitäts-Kinderklinik Göttingen)*: THE CARE OF THE NEWBORN OF DIABETIC MOTHERS. Deutsche Medizinische Wochenschrift 77:1069-74, September 5, 1952.

During the pregnancy period, diabetic women require an especially careful diabetes control in order to avoid diabetic coma as well as hypoglycemic conditions. In case of previous gestational toxicosis, hydramnios and stillbirths, hormone treatment should be considered. If

at all possible, the patient should be admitted during the 34th week of pregnancy, to a hospital where further treatment can proceed with the co-operation of the internists and obstetricians. The manner and time of parturition should not be dogmatically decided upon but should be completely dependent on the condition of the mother and child. Urgent indications for premature delivery by section are aged first-time mother, previous stillbirths, toxemia, and overgrowth or abnormal position of the child. The premature delivery, on one hand, and the peculiarities of the newborn of diabetic mothers make an immediate transfer of the infant to a pediatric department necessary; there, with close supervision, the difficulties to be expected can be met.

Heinsius, E. *(Hamburg, Germany)*: ON THE FREQUENCY, DISTRIBUTION AND ETIOLOGY OF THE CHANGES IN THE BACK OF THE EYE IN DIABETES MELLITUS. Deutsche medizinische Wochenschrift 77: 880-83, July 4, 1952.

On the basis of the author's observations of 1,000 diabetics, the increase in frequency of diabetic retinitis is pointed out and a statistically obtained distribution of retinal changes in diabetics is given. The etiology of retinal changes is discussed, and the damage to the various sections of the retinal vessels (capillaries, veins, arteries) is pointed out. Attention is called to the hormonal influences on the vessels, which must be considered particularly in diabetics.

Hellstrom, J. SURGICAL TREATMENT OF HYPERINSULINISM. Acta chirurgica scandinavica *103*:120, 1952.

The author reviews six cases of hyperinsulinism in which surgical procedures were done at a Stockholm hospital between 1944 and 1951.

Iannaccone, A.; D'Agostino, A. W.; and Siniscalco, M. *(Naples)*: PROBLEMS OF GENETICS IN DIABETES MELLITUS. Il progresso medico *8*:457, August 15, 1952 [*Abstr. from*: J.A.M.A. *151*:82, January 3, 1953].

The hereditary factors and the age of onset of diabetes mellitus were studied. It was revealed that when the diabetic was the offspring of two healthy parents, the disease was found in the collaterals of one of them. In some cases in which one parent was healthy and the other was diabetic, the disease was found in the collaterals of the healthy parent. Direct transmission from the parents to the children was found only in the first generation. Juvenile diabetes was rare and limited to children of two nondiabetic parents. These findings seem to confirm the hypothesis of recessive inheritance.

Jessar, Ralph A.; Horwitz, Orville; and Montgomery, Hugh *(Peripheral Vascular Sec. of the Robinette Foundation, Med. Clin., Hosp. of the Univ. of Pennsylvania, Philadelphia, Pa.)*: THE VASODILATOR EFFECTS OF INTRAVENOUS PROCAINE IN PATIENTS WITH ISCHEMIC EXTREMITIES. Am. J. M. Sc. *224*:300-03, September 1952.

Intravenous administration of clinical doses of 0.1 or 0.2 per cent procaine in Saline to 9 patients with peripheral arterial disease produced no significant change in digital cutaneous blood flow of fingers and toes, blood pressure, cardiac output, pulse rate, or oral temperature. Of the 9 patients whose ages ranged from 24 to 61 years, 4 had arteriosclerotic vascular disease, 3 Buerger's disease, 1 Raynaud's disease, and 1 increased vasomotor tone. In 4 patients undesirable side-effects of the procaine were noted.

Jones, Walter S. *(Providence Lying-In Hosp., Providence, R. I.)*: DIABETES IN PREGNANCY: A PRELIMINARY REPORT. Rhode Island M. J. *35*:662-68, December 1952.

The author concludes that the greatest single cause of fetal loss is acidosis, with or without toxemia. If acidosis and toxemia could be better controlled, the larger premature infants salvaged, and the routine accidents of delivery avoided, the present gross fetal loss would be materially reduced. A figure under 15 per cent should be attainable without the use of hormones. Hormone therapy offers little in the mild and in the uncomplicated diabetics. If the method has value, it would be in the older juveniles, the ten-year diabetics, and the older women. Discounting congenital anomaly and macerated fetus, the fetal salvage from cesarean section was not appreciably better than in vaginal delivery; the indication for section should be primarily obstetrical, except in selected cases.

Kade, Helmut; and Dietel, Hanns: PREGNANCY PROG-

NOSIS IN PREDIABETIC AND DIABETIC WOMEN. Deutsche medizinische Wochenschrift 77:673-75, May 23, 1952.

In addition to manifest diabetes, the prediabetic phase is also decisive for the fate of the pregnancy and of the child. Through diet and insulin treatment, the maternal mortality was considerably reduced. A further decrease is being promised by hormone therapy. It also is to be hoped that the infant mortality, which is still very high today, will be reduced by hormone therapy. However, even in the prediabetic phase, the number of complications during pregnancy and delivery is very high as compared with those in the healthy woman. The child mortality also is distinctly higher in the prediabetic period. The number of overweight and giant children did not differ, among the patients of these authors, between the prediabetic phase and the period of manifest diabetes.

Kaiser, Emil; Maxwell, L. C.; Landmann, W. A.; and Hubata, Robert *(Armour Laboratories, Chicago, Ill.)*: BIOLOGICALLY ACTIVE THIOCARBAMYL DERIVATIVES OF INSULIN. Arch. Biochem. *42*:94-101, January 1953.

Insulin was reacted with phenyl isothiocyanate and with allyl isothiocyanate. When these reactions were carried out in aqueous buffer solutions, biologically active phenylthiocarbamyl and allylthiocarbamyl insulin derivatives were obtained. Solubility properties, biological activity, and the amount of free amino groups were determined for a number of these insulin derivatives. A color reaction was applied to the identification of thiohydantoins. This reaction was also used in the paper chromatography of allyl- and phenylthiocarbamyl insulin hydrolyzates. The terminal amino acids involved in the reaction with the isothiocyanates were identified by their thiohydantoins in the chromatograms of the ether extracts of the hydrolyzates of the insulin derivatives. Complete agreement with Sanger's findings is reported.

Kim, K. S.; and Ivy, A. C. *(Dept. of Clin. Sci., Univ. of Ill. Coll. of Med., Chicago, Ill.)*: FACTORS INFLUENCING CHOLESTEROL ABSORPTION. Am. J. Physiol. *171*:302-18, November 1952.

On the basis of determining (a) the difference between dietary and fecal sterol levels and (b) serum cholesterol values, the authors report upon factors influencing cholesterol absorption and phospholipid excretion in rats. Fat facilitated cholesterol absorption when the dietary cholesterol:fat ratio in grams was 1:24 but not when the ratio was reduced to 1:8. The active factor promoting absorption was the fatty acid rather than the glycerol portion of the neutral fat molecule.

Fecal phospholipid excretion also varied with the diet. On a fat-free diet, only a trace was found. Addition of cholesterol or glycerol had no effect; but after an appreciable feeding of corn oil, phospholipids appeared in the feces and were further increased by administration of various free fatty acids, among which oleic acid was more effective than palmitic acid. The addition to the diet of the free fatty acids derived from corn oil increased the fecal phospholipid excretion 14 times more than did the equivalent amount of corn oil, so it is estimated that 7 per cent of corn oil fatty acids were split off in the intestine prior to absorption.

Cholic acid when added to the diet of rats receiving cholesterol and oleic acid significantly raised the serum cholesterol levels but this effect was slight with both cholic and desoxycholic acid in rats receiving cholesterol and corn oil. Desoxycholic acid was found to be more toxic in male than in female rats. A sex difference was also noted in the rate of body weight loss induced by feedings of thyroid. This weight loss was not prevented by feedings of cholesterol but was lessened by those of corn oil.

Krahl, M. E. *(Washington Univ. Sch. of Med.)*: INCORPORATION OF C^{14} AMINO ACIDS INTO PEPTIDES BY NORMAL AND DIABETIC RAT TISSUES. Science *116*:524, November 14, 1952.

In a study of the incorporation of glycine-l-C^{14} into glutathione as part of the investigation of the action of insulin in promoting the uptake of amino acids by the tissues, the author reports the favorable influence exerted by insulin is due mainly to its favorable effect on glucose utilization.

Lazarus, Sydney S.; and Volk, Bruno W. *(Div. of Laboratories, Jewish Sanitarium and Hosp. for Chronic Diseases, Brooklyn)*: THE EFFECT OF PITUITARY GROWTH HORMONE ON THE INSULIN TOLERANCE OF THE ADRENALECTOMIZED DOG. Metabolism *1*:355-62, July 1952.

The adrenalectomized dog has a fasting blood sugar concentration that is markedly lower than that of the intact animal. The intravenous injection of 0.1 unit of

crystalline insulin per kilogram of body weight into such an animal is followed by a progressive, uninterrupted decline of the blood sugar level. The subcutaneous administration of 1 mg. per kilogram of growth hormone into the fasted adrenalectomized dog two hours before the injection of insulin causes no change in the fasting blood sugar level or in the response to insulin. However, when such animals are pretreated with the same amount of growth hormone on each of three days, the fasting blood sugar returns to a normal level, and an insulin tolerance curve similar to that of the normal dog is observed. When the pretreatment with growth hormone is prolonged or the dosage is increased, the fasting blood sugar remains close to the normal, but there is a marked rèduction of insulin sensitivity. These observations lead to the conclusions that the anti-insulin action of growth-hormone pretreatment is independent of the adrenal cortex and that a sufficient time interval must elapse for some unknown intermediary changes to take place for this effect to become apparent.

Kjems, E. VARIATIONS IN NUMBER OF CIRCULATING EOSINOPHIL CELLS IN DIABETIC PATIENTS. Ugeskrift for Laeger *114*:924-28, July 10, 1952.

In diabetic patients treated with insulin, high and widely fluctuating eosinophil counts were found, perhaps as an expression of variations in the function of the adrenal cortex.

Lawrence, R. D. *(London, England)*: LIPODYSTROPHY AND LIPO-ATROPHY. Brit. M. J. 2:1355, December 20, 1952.

The author, in a short letter, stresses the difference between lipodystrophy and lipo-atrophy and the lack of factual knowledge concerning these conditions with regard to their etiology.

Leevy, Carroll M.; O'Connell, William; and White, Thomas J. *(Dept. of Med., Jersey City Med. Center, Jersey City, N. J.)*: CARBOHYDRATE DISTURBANCES IN LIVER DISEASE. J. M. Soc. New Jersey 50:44-49, February 1953.

Carbohydrate tests are valuable in the study of patients with liver disease when correlated with other clinical data. Patients with liver disease may have a normal fasting blood sugar, hypoglycemia, or hyperglycemia. Hypoglycemia usually responds readily to a high-carbohydrate intake. Hyperglycemia due to diabetes mellitus requires insulin in addition to a proper diet. Blood sugar elevation due to hepatic disease may respond to a high-carbohydrate, high-protein diet without insulin.

Long, C. *(Dept. of Biol. Chem., Univ. of Aberdeen, Scotland)*: STUDIES INVOLVING ENZYMIC PHOSPHORYLATION. 2. CHANGES IN THE HEXOKINASE ACTIVITY OF THE SMALL INTESTINE OF RATS CAUSED BY FEEDING DIFFERENT DIETS. Biochem. J. 53:7-12, January 1953.

The hexokinase activities of intestinal mucosa homogenates from rats fed on different diets for 8 months after weaning have been determined. Highest activity was found in rats fed a fat-free diet and lowest in those fed a high-fat diet. Intermediate values were obtained in rats fed basal (balanced) and high-protein diets. Alkaline phosphatase activities of intestinal mucosa showed no significant differences. Rats fed for only 1 or 2 weeks on high-fat diets and fat-free diets also showed statistical differences in the hexokinase activities of their intestinal mucosae. No differences were found between hexokinase activities of intestinal muscle of the two groups.

Loveless, Mary Hewitt; and Cann, John R. *(New York Hosp. and Dept. of Med., Cornell Univ. Med. Coll., New York, and Dept. of Biophysics, Univ. of Colorado Med. Center, Denver, Colo.)*: DISTRIBUTION OF ALLERGIC AND "BLOCKING" ACTIVITY IN HUMAN SERUM PROTEINS FRACTIONATED BY ELECTROPHORESIS CONVECTION. Science *117*:105-08, January 30, 1953.

The authors report upon the fractionation of allergic antibodies in human serum proteins by electrophoresis convection and upon the immunologic and electrophorectic characterization of the fractions obtained. Electrophorectic convection was extended to 7 stages, and a technique of serial dilution of the immunologically active material was employed in carrying out the activity tests by the "passive transfer" procedure after neutralization of the allergen in vitro. Study of a woman highly allergic to all preparations of commercial insulin revealed the skin-sensitizing power against insulin to be associated almost exclusively with the beta-globulin fraction. Study of a serum containing reagins for ragweed pollen revealed activity to be distributed through the

gamma and beta-globulins, and a thermo-stable component (blocking antibody) of this activity was concentrated in the gamma-globulins.

Lueth, Harold C.; and Freidell, Hugh V. *(Dept. of Int. Med., Univ. of Nebraska Coll. of Med., Omaha)*: TREATMENT OF SEVERE DIABETIC ACIDOSIS. Nebraska M.J. 37:277-80, September 1952.

The essentials in the treatment of severe diabetic acidosis consist in the prompt correction of the acidosis, reduction of hyperglycemia, relief of the dehydration, and restoration of electrolyte balance. Diabetic acidosis is preventable, and physicians should warn their patients of the seriousness of the condition and advise measures that will avoid its appearance.

Lumb, George; and Beautyman, William *(Dept. of Path., Westminster Med. Sch., London, England)*: HYPOPLASIA OF THE EXOCRINE TISSUE OF THE PANCREAS. J. Path. & Bact. 64:679-86, October 1952.

Two cases of hypoplasia of the exocrine tissue of the pancreas are reported, the first to be described in siblings. Histologic differences between this condition and fibrocystic disease of the pancreas are discussed. In contrast to fibrocystic disease, there is no evidence of abnormality of the secretion of the pancreas or any other gland. A small number of similar cases which have been described in medical literature are briefly discussed. Etiology remains obscure; and, whereas at the present time some developmental abnormality seems to be the most likely cause, the possibility of an inflammatory background must be seriously considered. Pancreatic changes following Coxsackie-virus infection in mice are discussed in this connection.

MacQueen, A. T. *(Physiology Dept., Univ. Coll., Dundee, Univ. of St. Andrews)*: THE EFFECT OF ALLOXAN INTRAVENOUSLY ON THE BLOOD PRESSURE OF THE RABBIT. J. Physiol. 118:9P-10P, October 28, 1952. [*Abstr. from* paper presented at meeting of the Physiological Society, Physiological Department, University New Buildings, Edinburgh, July 4-5, 1952].

It has been found that alloxan produces a sudden transient rise in blood pressure in the rabbit, even in doses well below the diabetogenic. This response is not abolished by decerebration, hypophysectomy, adrenalectomy, or nephrectomy. It is not prevented by previous administration of dibenamine or hexamethonium bromide; nor is it prevented by dimercaprol (B.A.L.) given to protect against the diabetogenic effects of this substance.

Madonick, M. J.; and Margolis, J. *(New York City)*: PROTEIN CONTENT OF SPINAL FLUID IN DIABETES MELLITUS: REPORT ON ONE HUNDRED CASES. A.M.A. Arch. Neurol. & Psychiat. 68:641-44, November 1952.

The authors' results show that an increase in the cerebrospinal-fluid protein is found in diabetes mellitus only when neurologic complications are present; the most common complication with an increase in the spinal-fluid protein concentration was peripheral neuropathy.

Mayer, J.; Bates, Margaret W.; and Van Itallie, Theodore B. *(Dept. of Nutrition, Harvard Sch. of Pub. Health, Boston)*: BLOOD SUGAR AND FOOD INTAKE IN RATS WITH LESIONS OF THE ANTERIOR HYPOTHALAMUS. Metabolism 1:340-48, July 1952.

Rats made hyperphagic by means of lesions in the anterior hypothalamus were studied from the standpoint of nonfasted levels of blood glucose. A number of rats with lesions of the anterior hypothalamus which failed to display frank hyperphagia also were studied. Levels of circulating eosinophils were determined, and the effect of corticotropin and of nonspecific stress stimuli on the food intake of the hyperphagic animals was observed. Some insulin sensitivity studies were done. An excellent degree of correlation could be established when nonfasted blood glucose levels were related to food intake as measured by rates of weight gain. Alternate theories to explain this relationship are discussed, including application of the "glucostatic" concept of the regulation of food intake.

Mirsky, I. Arthur; Futterman, Perry; Rubenstein, Edward; and Haft, David E. *(May Inst. for Med. Res. of the Jewish Hosp. and the Dept. of Med., Coll. of Med., Univ. of Cincinnati)*: DIABETES DETECTION SURVEY AMONG MALE PHYSICIANS. Metabolism 1:307-13, July 1952.

Three hundred sixty-two male and 22 female physicians, comprising 37 per cent of the medical population of Cincinnati, presented themselves for a "diabetic survey."

Of these, 4 were known to have diabetes mellitus, and in 2 others a mild form of this syndrome was diagnosed. Of the 358 male physicians with no previous evidences of metabolic derangements, 30.4 per cent reported a history of diabetes in some member of the family. Further analysis revealed a positive family history of diabetes in 42.9 per cent of the Jewish physicians and in 20 per cent of the non-Jewish physicians.

Morrison, Lester M. *(Los Angeles, Calif.)*: DIET AND ATHEROSCLEROSIS. Ann. Int. Med. 37:1172-89, December 1952.

The reports from various countries during World War II years of the influence of a low-fat, low-cholestrol diet on reducing the mortality rate from coronary artery disease are reviewed. Fat and cholesterol intake in the diet appears to be related statistically to the incidence of death from coronary atherosclerosis.

Najjar, Victor A. *(Dept. of Pediat., Johns Hopkins Univ. Sch. of Med., Baltimore, Md.)*: THE PHYSIOLOGY AND DISORDERS OF CARBOHYDRATE METABOLISM. J. Pediat. *41*:804-14, December 1952.

The author has written an exceptionally good article bringing together the pertinent contributions made in the basic science of carbohydrate metabolism and relating them to clinical problems. The paper is limited to those enzyme systems of carbohydrate metabolism that have a direct bearing on clinical problems. The discussion involves the following categories: (1) The key enzymes that take part in the transformation of glucose to glycogen and vice versa. (2) The influence of hormones upon these systems. (3) Diseases of carbohydrate metabolism and possible interpretation of the metabolic defect in terms of the role of enzymes and hormones.

Nikkilä, Esko; and Oker-Blom, Nils. *(Dept. of Med. Chem. and Dept. of Serology and Bact., Helsinki Univ., Finland)*: ABSORPTION OF SERUM LIPIDS BY MONTMORILLONITE. Science *116*:685-86, December 19, 1952.

The authors report that montmorillonite absorbs all the cholesterol, 80 to 85 per cent of the phospholipids, and 15 to 20 per cent of the proteins from serum; therefore, the clay can be used for the removal of lipid-containing material from different sources as well as for investigations concerned with the interactions between lipids and proteins.

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de Ocampo, Geminiano. CATARACT EXTRACTION IN DIABETES MELLITUS. Acta medica Phillippina 8:113-20, Ocober-December 1951.

In 36 cases of senile cataract in elderly diabetics the results of cataract extraction compared favorably with those in nondiabetic subjects. The author considers a blood sugar level of 150 to 160 mg. to be optimal.

Page, Otto C. *(Univ. of Oregon Med. Sch., Portland)*: CLINICAL APPLICATION OF A SIMPLE QUALITATIVE SERUM ACETONE TEST IN DIABETES MELLITUS. New England J. Med. *248*:295-97, February 12, 1953.

The technic, interpretation, and clinical applications of the simple nitroprusside qualitative test for serum or plasma acetone are re-evaluated. Simultaneous determinations of serum carbon-dioxide content and quantitative blood ketone levels in a limited number of cases are discussed.

When a "four plus" serum acetone reaction is found in a patient who has not received treatment for diabetic acidosis, the carbon-dioxide content is usually 10 mEq. or less per liter, and there is a minimum of about 40 mg. per 100 cc. of total ketone bodies in the whole blood.

A "two plus" or "three plus" reaction is usually accompanied by carbon-dioxide values between 10 and 20 mEq. per liter. A trace or "one plus" reaction seems to be accompanied by carbon-dioxide values in the normal range or only slightly depressed.

It is pointed out that the test is not simply a substitute for plasma carbon-dioxide determinations; it may yield additional information of aid in the evaluation and treatment of the acutely ill diabetic patient.

Paul, Jerome T. *(Univ. of Illinois Coll. of Med., Chicago, and St. Francis Hosp., Evanston)*: CHARCOT JOINT IN DIABETES MELLITUS. Am. Pract. 4:49-51, January 1953.

Two cases of Charcot's joint in diabetes mellitus are reported. In both cases the destructive bony lesions were associated with peripheral neuritis, impaired circulation, and chronic infection in soft adjacent tissues.

Ricketts, Henry T. *(Dept. of Med., Sch. of Med., Univ.*

of Chicago): BASIC PRINCIPLES IN THE THERAPY OF DIABETES. Ann. Int. Med. *37*:1181-87, December 1952.

The relief of symptoms and the achievement and maintenance of normal nutrition are objectives which can be easily realized in co-operative patients by the appropriate use of diet and insulin. Available evidence indicates that the preservation of the insulin-producing power of the pancreas and the mitigation of infections, metabolic, and degenerative complications are materially aided, if not fully accomplished, by the proper control of hyperglycemia and glycosuria.

Peterson, John H. *(Duluth, Minn.)*: COMMON OCULAR MANIFESTATIONS OF DIABETES MELLITUS. Minnesota Med. *36*:45-48, January 1953.

The author reviews the literature and describes the changes which are seen in all structures of the eyes of patients with diabetes mellitus. He points out that the more serious changes are those which occur in the retina but that changes in the lens are probably more frequent and changes in refraction are also known.

Queries and Minor Notes *(Illinois)*: DUODENAL ULCER. J.A.M.A. *151*:599, February 14, 1953.

There is no relationship between blood sugar levels and duodenal ulcer and no evidence that indicates that patients with duodenal ulcer have a low blood sugar level. On the contrary, diabetes and duodenal ulcer can occur in the same person.

Rafsky, Henry A.; Brill, Alton A.; Stern, Kurt G.; and Corey, Harold *(Geriatric Inst. of the Hosp. and Home of the Daughters of Jacob, Bronx, N. Y., Polytechnic Inst., Brooklyn, N. Y.)*: ELECTOPHORETIC STUDIES ON THE SERUM OF "NORMAL" AGED INDIVIDUALS. Am. J. M. Sc. *224*:522-28, September 1952.

Electrophoretic study of the blood serum of "normal" human subjects whose ages ranged from 65 to 95 years revealed that the protein distribution in the serum of the aged individuals differs significantly from that of younger subjects with regard to A/G ratio, relative albumin, and beta-globulin concentrations; the first two are smaller and the third is greater in the older age group.

Ramfjord, Sigurd *(Sch. of Dent., Univ. of Michigan, Ann Arbor)*: CLINICAL AND HISTOLOGIC EFFECTS OF ALLOXAN IN RHESUS MONKEYS. Am. J. Clin. Path. *22*:745-54, August 1952.

Ten rhesus monkeys were injected with alloxan. Toxic changes produced by alloxan were found in the liver, kidneys, and pancreas. The hyperglycemic state that developed following injection of alloxan and the toxic changes seen in the liver appeared to be related. The initial hyperglycemia following an injection of alloxan may be explained as the first reaction to the toxic influence of alloxan upon the liver. Toxic changes in the kidneys resulted in glomerulonephrosis. The pancreatic changes were comparable to those reported in the literature. The hepatorenal syndrome may explain the death of the hypoglycemic animals. No oral, peridontal, or bone changes were observed in monkeys with alloxan diabetes.

Reinecke, Roger M. *(Dept. of Physiol. and Pharmacol., Univ. of Puerto Rico Sch. of Med., San Juan, Puerto Rico)*: RENAL GLUCOGENESIS IN THE EVISCERATED MONKEY (MACACA MULATTA). Am. J. Physiol. *171*: 29-31, October 1952.

In a study carried out on 11 animals, the concentration of sugar was found in the eviscerated monkey to be greater in blood from the renal vein than in blood from the artery.

Roberts, James E.; Anderson, Leighton L.; and Parry, Thomas M. *(Univ. of Colo. Sch. of Med., Denver, Colo.)*: THE CLINICAL EFFECTIVENESS OF CERTAIN OF THE HYDROGENATED ALKALOIDS OF ERGOT IN PERIPHERAL VASCULAR DISORDERS. Am. J. M. Sc. *224*:431-38, October 1952.

The authors report upon the oral administration, 0.5 mg. or 1 mg. t.i.d., of hydergine (CCK—179), a mixture of three dihydrogenated ergot alkaloids, dihydroergocristine, dihydroergocornine, and dihydroergotkryptine, to 72 patients with peripheral vascular disease.

Thirty-five patients had arteriosclerotic vascular disease; 6, Buerger's disease; 8, Raynaud's syndrome; 13, acute thrombophlebitis; and 10, chronic venous insufficiency. Significant improvement was noted in those patients with organic arterial peripheral vascular disease, particularly those with ulcerative lesions, but not in those with functional arterial involvement. Toxic and side-effects were rare.

Salo, Torsti P. *(Dept. of Chem., Univ. of Tennessee, Knoxville, Tenn.)*: METHODS FOR THE DETERMINATION OF BLOOD SUGAR BASED ON THE PERIODATE REACTION. Arch. Biochem. *42*:106-13, January 1953.

Of the many methods for the determination of blood glucose, none is based on a stoichiometric reaction between the glucose and the oxidizing agent. Glucose, other carbohydrates, and the hexitols, however, are known to react with periodate in neutral or acid solution in stoichiometric proportions. The present communication describes an application of the periodate reaction with glucose for the measurement of glucose concentrations in blood by both colorimetric and titrimetric methods. The results on tungstic acid filtrates with the new methods are lower than with the standard clinical procedures, but higher than results on filtrates which represent "true" blood glucose levels.

Scherr, George H. *(Dept. of Microbiology, The Creighton Univ. Sch. of Med., Omaha, Nebr.)*: THE EFFECT OF ENVIRONMENTAL TEMPERATURE ON CORTISONE FOR MICE. Science *116*:685, December 19, 1952.

In mice, the toxic effects of cortisone are enhanced by temperature; these temperature effects must be controlled in experimental investigations and might be significant in the clinical use of the drug.

Schept, Samuel S. *(Union City, N. J.)*: IMPOTENCE AND DIABETES. J.A.M.A. *150*:1361, November 29, 1952.

There are no reliable data available as to whether the complaint of inability to obtain an erection is commoner in diabetic than in nondiabetic males. In this connection, distinction must be made between the symptom mentioned and basic infertility due to impaired spermatogenesis. Psychological factors are often of great importance, as they are in nondiabetics. Testosterone in dosage of 5 to 25 mg. intramuscularly at two to five-day intervals has been recommended, but its value is equivocal. Other forms of treatment recommended but also of uncertain value are the use of thyroid extract in dosage of 60 to 180 mg. daily, the weekly instillation of 5 cc. of 0.5 per cent silver nitrate solution into the prostatic urethra, and a course of prostatic massage. Careful and continuous control of the diabetic condition, an adequate diet, the avoidance of excessive physical and emotional fatigue, and psychotherapy are indicated.

Setlow, Richard; and Doyle, Barbara *(Biophysics Div., Sloane Phys. Lab., Yale Univ., New Haven, Conn.)*: THE MOLECULAR WEIGHT OF INSULIN AND THE INACTIVATION OF INSULIN BY FAST CHARGED PARTICLES. Arch. Biochem. *42*:83-90, January 1953.

The inactivation of dry amorphous insulin by deuterons and electrons indicates that the unit of hormonal activity is roughly spherical and of molecular weight 23,000. The changes in the absorption spectrum of dry insulin after deuteron bombardment are similar to those found with ultraviolet inactivation.

Shuman, Charles R. *(Temple Univ. Sch. of Med. and Hosp., Philadelphia, Pa.)*: NOCTURNAL CRAMPS IN DIABETES MELLITUS: CLINICAL AND PHYSIOLOGICAL CORRELATIONS. Am. J. M. Sc. *225*:54-60, January 1953.

The author reports that the use of quinine sulphate in the treatment of nocturnal leg cramps was effective in 23 of 30 diabetic patients with this complaint.

The occurrence of leg cramps was unrelated to the degree of metabolic control, age or weight of the patient, duration of diabetes, or the level of carbohydrate intake.

Treatment directed toward vascular or neuropathic complications found in 12 patients did not relieve their muscle cramps.

The administration of quinine, 0.3 gm. orally, at bedtime, produced freedom from the symptoms after 1 or 2 doses. Following the nightly administration of quinine for 7 to 10 doses, no recurrence of muscle cramps within a period of 6 months was noted, except in the case of one patient who required further treatment after 2 months.

Since the relaxation of muscle depends upon available energy for the unfolding of actin-myosin links within muscle fibers, it is suggested that the defect responsible for muscle cramps may lie in the failure of the formation of chemical energy or in storage of energy within the tissues.

Quinine and antihistaminics may prevent tetanic contraction by inhibiting the release of available energy under certain conditions.

Siegel, Ralph *(Perth Amboy, N. J.)*: DIABETIC RETINOPATHY WITH SPECIAL REFERENCE TO JUVENILE

DIABETES. J. M. Soc. New Jersey *49*:402-05, September 1952.

Diabetic retinopathy is increasing steadily in frequency and is occurring at an earlier age. Retinal atherosclerosis is the most common finding in the young patient with dibetes of ten or more years. Atherosclerosis, changes in the venous capillaries, excess deposition of fat and hypoproteinemia with metabolic consequences of edema, and hyalin deposition are probable causative factors in diabetic retinopathy. To this array may be added blood sludging in the retinal veins, noted in one case in this report. Up to the present time, the prophylaxis of rigid control and the use of lipotropic substances offer the best prognosis.

Slater, E. C. (*Dept. of Pharmacol., N.Y.U. Sch. of Med., and Molteno Inst., Univ. of Cambridge, England*): SPECTROPHOTOMETRIC DETERMINATION OF FRUCTOSE -1:6-DIPHOSPHATE, HEXOSEMONOPHOSPHATES, ADENOSINETRIPHOSPHATE AND ADENOSINEDIPHOSPHATE. Biochem. J. *53*:157-67, January 1953.

An enzymic method for the determination of phosphorylated sugars and energy-rich compounds is described. The method depends upon the enzymic conversion of these compounds to dihydroxyacetone-phosphate, which then reacts with reduced DPN in the presence of glycerol-phosphate dehydrogenase. The amount of reduced DPN reacting is determined spectrophotometrically. The method is highly sensitive, 0.05 μ mole of phosphorylated sugar or energy-rich phosphate being measured within an accuracy of a few per cent. In a complex mixture separate analyses are obtained for (a) hexosediphosphate + triosephosphates, (b) hexosemonophosphates (glucose-6-phosphate, glucose-1-phosphate, fructose-6-phosphate, but not fructose-1-phosphate), (c) adenosine triphosphate, and (d) other energy-rich compounds (adenosine diphosphate, creatine phosphate, phosphopyruvate [which is overestimated by 50 per cent]). The only substances which interfere are (i) pyruvate and oxaloacetate, each molecule of which reacts as one-half a molecule of hexosediphosphate, and (ii) phosphoglycerate, which behaves like phosphopyruvate. Pyruvate and oxaloacetate may be separately determined with lactic and malic dehydrogenases. Analyses of preparations of phosphorylated sugars and adenine nucleotides, either prepared in the laboratory or obtained commercially, have been made both by the new method and by conventional chemical methods. Agreement was very close in most cases. Disagreement has been traced to the presence in the preparations of impurities which are estimated by the chemical but not by the enzymic method.

Smith, M. J. H. (*Dept. of Chem. Pathol., King's College Hosp. Med. Sch., London, England*): THE EFFECT OF SALICYLATE ON THE GLYCOSURIA AND HYPERGLYCEMIA INDUCED BY CORTISONE IN THE NORMAL RAT. Biochem. J. *52*:649-52, December 1952.

The effects of salicylate on the glycosuria and hyperglycemia induced by cortisone in the normal rat and of cortisone with and without salicylate on the blood glucose and liver glycogen of the adrenalectomized rat have been studied. Salicylate reduces the glycosuria and hyperglycemia induced by cortisone in the normal rat. Cortisone causes deposition of liver glycogen in the adrenalectomized rat, whereas the concurrent administration of salicylate produces not only depletion of existing glycogen but also prevents the deposition of new glycogen by the cortisone. The implications of these effects of salicylate are discussed.

Smolen, Elwyn M. (*Med. Dir., Bridgeport Soc. for Mental Hygiene*): AN EVALUATION OF PSYCHOSOMATIC MEDICINE. Connecticut M. J. *17*:3-17, January 1953.

The author lists so-called psychosomatic disorders including in the endocrine group 1) alterations in the amount of adrenal, pituitary, thyroid, and pancreatic secretions in anxiety; 2) functional hyperglycemia and glycosuria; 3) hyperinsulinism in emotional tension; 4) hyperthyroidism; and 5) diabetes mellitus.

Sparks, M. Irving *(Cleveland)*: TREATMENT OF LATE COMPLICATIONS OF DIABETES. Am. Pract. *4*:9-11, January 1953.

In the treatment of diabetic retinitis the author recommends the use of a high-protein diet. In diabetic neuritis he favors Treatment with B.A.L.

Stein, Jerome D., Jr.; Bennett, Leslie L.; Batts, Adrienne A.; and Li, Choh Hao. (*Dept. of Physiol., Inst. of Exper. Biol. and Dept. of Biochem., Univ. of California, Berkeley, Calif.*): SODIUM, POTASSIUM AND CHLORIDE RETENTION PRODUCED BY GROWTH HORMONE IN THE

ABSENCE OF THE ADRENALS. Am. J. Physiol. *171*:587-91, December 1952.

Intraperitoneal administration of 1 mg. daily of growth hormone (free of antidiuretic activity) produced retention of potassium, sodium, chloride, and nitrogen in adrenalectomized rats both with and without simultaneous administration of adrenal cortical extract (ACE). During the 3-day period of administration, there was persistent retention of nitrogen and potassium, but that of sodium and chloride was only transient. At the conclusion of an experiment, completion of adrenalectomy was substantiated by demonstrating the animal's inability to survive a high intake of potassium on discontinuing ACE maintenance therapy. The above effects of growth hormone, therefore, are not mediated through the adrenal cortex.

Steiner, Robert F. (*Nav. Med. Res. Inst., Bethesda, Md.*): REVERSIBLE ASSOCIATION PROCESSES OF GLOBULAR PROTEINS. I. INSULIN. Arch. Biochem. *39*:333-54, August 1952.

Since the discovery of the dissociation of the insulin tetramer by Gutfreund, this phenomenon has aroused a good deal of interest. As insulin is a well-studied protein, the molecular characteristics of which are accurately known, it serves as an ideal simplified case in which the general principles involved in reversible protein associations may be studied. The early work cited above has clearly established the phenomenon and produced some valuable qualitative information on the influence of conditions. However, little progress has been made in the direction of a theoretical understanding of the process or even of quantitatively accounting for the data in terms of equilibrium constants. Agreement now appears to be general that the basic molecular unit of insulin has a molecular weight close to 12,000, the best present estimate being 11,500. It has been shown that, in solution, association to polymers as high as the tetramer, or perhaps higher, occurs. It must be kept in mind that the possibility exists of some variation in the dissociation characteristics of different lots of insulin and that, indeed, there is some evidence that this is the case. In any event the more qualitative conclusions will presumably be valid for all preparations. The dissociation of insulin is favored by (a) an increase in charge, (b) a decrease in ionic strength, and (c) an increase in temperature. The dissociation curves may be fitted best with stepwise constants. The heat of dissociation falls with increase of charge. Evidence is presented for the presence of aggregates as high as the pentamer.

Stewart, Charles T.; Salmon, Robert J.; and May, Charles D. (*Coll. of Med. Sciences of Univ. of Minnesota and State Univ. of Iowa*): FACTORS DETERMINING EFFECT OF INSULIN ON METABOLISM OF GLUCOSE IN ASCORBIC ACID DEFICIENCY AND SCURVY IN THE MONKEY. A.M.A. Am. J. Dis. Child. *84*:677-91, December 1952.

The effect of ascorbic acid deficiency on adrenocortical function was studied; observation of the effect of insulin on the level of glucose in the blood was chosen as a test of adrenocortical function. It was found that the dose of insulin which produced a pronounced depression of blood glucose in control monkeys had little effect in scorbutic monkeys. The data obtained indicate that adrenocortical function is increased in scurvy rather than decreased and that this accounts for the relative lack of effect of insulin on blood glucose in scurvy.

Stewart, H. B.; and Young, F. G. (*Sir William Dunn Inst. of Biochemistry, Cambridge, Eng.*): A SUBSTANCE IN ANIMAL TISSUES WHICH STIMULATES KETONE-BODY EXCRETIONS. Nature *170*:976-77, December 6, 1952.

When a ketonic substance from muscle is fed or administered by stomach tube to rats receiving the casein-containing high-fat diet, an increase in ketonuria lasting some days is consistently observed. It has not yet been possible to produce a response as great as that observed in animals receiving horse meat in place of casein. It seems likely that most, if not all, of the urinary ketone bodies excreted by rates receiving a high-fat diet supplemented with meat protein result from the activity of a nonprotein component of the meat. The study, in which both alloxan-diabetic and normal rats were used, indicates that this metabolic factor exerts its effect in normal as well as in diabetic animals. The chemical nature of this substance and the means whereby it alters the metabolic pattern are under investigation.

Stirland, Gordon B.; and Crossen, George E. (*Sch. of Pharm., Oregon State Coll., Corvallis*): FORMULATION OF PHARMACEUTICALS FOR THE DIABETIC: 1. PRELIMINARY STUDIES IN THE INDUCTION OF ALLOXAN DIABETES IN RABBITS. J. Am. Pharm. A. (Scient. Ed.) *61*:609-11, November 1952.

Results obtained in this study indicate that alcohol, in the amount of 0.45 cc./kg., does not influence blood sugar concentration in either normal or diabetic rabbits to any greater extent than does water. Sudden rises in the level of blood sugar noted after administration of alcohol are also noted following administration of water. This phenomenon was attributed to the emotional response of the animal, which made it difficult to ascertain the effect of the material administered. Fluctuations attributed to emotional response in the diabetic rabbits were of a greater magnitude than those in the normal animals, since the blood sugar level in diabetics is not controlled to the same extent as in normal animals. The method used here for induction of diabetes in rabbits was found to be reliable; the greatest difficulty arose in the loss of some animals during unsupervised periods. Likewise, the other methods employed in this study could be applied to a standardized procedure if the exceptions noted could be overcome.

Texter, Clinton E., Jr.; Redisch, Walter; Sheckman, Edward; Ferguson, Shirley; and Steele, J. Murray. (*Res. Ser., Third (N. Y. Univ.) Med. Div., Goldwater Mem. Hosp., Welfare Is., and the Dept. of Med., N. Y. Univ. Coll. of Med., New York, N. Y.*): EVALUATION OF VASODILATOR DRUGS IN FOUR PATIENTS WITH ARTERIOSCLEROSIS OBLITERANS. Am. J. M. Sc. *224*:408-12, October 1952.

The authors report upon the response of intermittent claudication, night cramps, claudication time, and skin temperature to the oral administration of Pronestyl, Roniacol, Priscoline, and a new adrenergic blocking agent SKF 688A in 4 male patients with arteriosclerosis obliterans.

Intermittent claudication and night cramps were improved with Roniacol and Priscoline and to a lesser degree with SKF 688A. No effect was noted with Pronestyl.

The claudication times were significantly lengthened in only 2 of the 4 patients on Roniacol, Priscoline, and SKF 688A. There was no change with Pronestyl.

The skin temperature of the great toes was elevated in all of the 3 patients tested on SKF 688A; and in 2 of the 3 tested on Roniacol and on Priscoline.

No single test seems adequate to describe vasodilator effect.

Thosteson, George C. (*Detroit*): OFFICE MANAGEMENT OF DIABETES. Harper Hosp. Bull. *11*:18-23, January-February 1953.

The word "diabetes" usually strikes terror in the average person. The physician should anticipate and dispel this attitude by spending time explaining the nature of the disease to the patient. He should point out that diabetes carries no outward stigma. It is one of the few chronic diseases with which the patients can remain economically and socially active. The physician's attitude should be calm and reassuring. The general program should be outlined; namely, a diet that is quite liberal, insulin when and if necessary, and periodic and regular visits to the doctor. The management of diabetes requires some degree of regimentation. It is a nuisance disease, and advice to the patient should avoid rigid restrictions and unnecessary inconveniences.

Tonks, D. B. (*Dept. of Natl. Health and Welfare, Ottawa, Canada*): AN IMPROVED TECHNIC FOR BLOOD GLUCOSE BY THE FOLIN-WU METHOD WITH AN APPRAISAL OF OTHER MODIFICATIONS. Am. J. Clin. Path. *22*:1009-17, October 1952.

A modification of the Folin-Wu method for the determination of blood sugar is outlined and compared with the original procedure. The proposed modification has several important advantages over the regular Folin-Wu method. The final color is remarkably stable, and readings may be made at any time within several hours after dilution. The method is not sensitive to slight changes in technic, and only the heating periods need be exactly timed. These improvements enable the technician to handle, without strain, many more samples than formerly. Since the time of exposure is lessened by 3 minutes, chances for oxidation of the cuprous oxide are reduced. Bubble formation, an annoying feature of the old procedure, is completely eliminated by the reheating; the same sugar values are obtained by the modified and regular procedures, and the same reagents are used.

Tribby, C. L. (*St. Vincent's Hosp., Bridgeport, Conn.*): EFFECT OF ADRENOCORTICOTROPIC HORMONE (ACTH) ON SERUM AMYLASE ACTIVITY AND CARBOHYDRATE METABOLISM. Am. J. Clin. Path. *22*:855-59, September 1952

Twenty patients with rheumatoid arthritis were given 40 mg. of ACTH in two doses. Carbohydrate metabolism, as reflected by the glucose tolerance test, was signifi-

cantly decreased in 60 per cent of the patients 24 hours after the therapeutic dose of ACTH. Serum amylase determinations show a close correlation with glucose tolerance tests and are supplementary evidence in the evaluation of carbohydrate metabolism in patients treated with ACTH.

Twiss, Russell J.; and Carter, Franklin R. (*Depts. of Med. and Surg., New York Univ. Post-Grad. Med. Sch.: Fourth Med. and Surg. Divs., New York Univ., Bellevue Hosp.; and University Hospital, New York, N. Y.*): THE RELATIONSHIP OF BILIARY TRACT DISORDERS TO DIABETES MELLITUS. Am. J. M. Sc. *224*:263-73, September 1952.

The authors present a review and summary of their own experience emphasizing the frequent occurrence and failure to recognize biliary tract and pancreatic disease in diabetic patients, with the former diseases bearing an etiologic relationship to or intensifying a pre-existing diabetes.

Werthessen, N. T.; and Schwenk, E. (*Worcester Foundation for Experimental Biol., Shrewsbury, Mass.*): BIOSYNTHESIS OF CHOLESTEROL: FACTORS REGULATING BIOSYNTHESIS OF CHOLESTEROL-LIKE SUBSTANCES IN ISOLATED WHOLE LIVERS. Am. J. Physiol. *171*:55-61, October 1952.

In the perfusion of surviving livers with C_{14}-acetate, damage to the organ plays an important part in the efficiency of the biosynthesis of C_{14}-cholesterol. Livers mounted in the perfusion system with the least possible damaged converted a minimum of labeled acetate to labeled cholesterol. Additional damage, like cission of the organ, multiple puncturing of its surface, or administration of bacterial toxins or bacteria to the perfusion, system, increased the isotope concentration in the C_{14}-cholesterol.

There are two concepts which could explain the results observed: 1) Damage to the liver may harm the mechanisms which convert newly formed cholesterol into other products or which destroy it. 2) Damage to the liver may stimulate the mechanisms which synthesize cholesterol from simpler substances, such as acetate. The data as presented in this investigation are not adequate to permit a distinction between these two possibilities.

Wilens, Sigmund L.; and McCluskey, Robert T. (*Depts. of Pathol., Bellevue Hosp. and New York Univ. College of Med., New York, N. Y.*): THE COMPARATIVE FILTRATION PROPERTIES OF EXCISED ARTERIES AND VEINS. Am. J. M. Sc. *224*:540-47, November 1952.

The filtration properties of excised human iliac arteries and veins were tested with human blood serum and other fluids. Both types of vessels were found to be freely permeable to small molecular substances, such as the inorganic constituents of serum. Both were impermeable to large molecular substances, such as the cholesterol of egg yolk solutions and India ink.

Substances of intermediate molecular size, for example, hemoglobin, serum albumen, globulin, and cholesterol, did not filter completely through both excised arteries and veins. The amount that filtered varied inversely with the molecular size of these colloidal substances. Much larger fractions were consistently found in venous rather than in arterial filtrates.

The rate of filtration of serum and other fluids through excised veins is much more rapid than through arteries. Filtration of serum through veins occurs at minimal positive pressures but does not occur through arteries at pressures of less than 20 mm. Hg.

The differences in permeability of veins and arteries to colloids is indicated by dialysis experiments. The greater retention of serum colloids within the lumen of the artery causes a higher colloidal osmotic pressure than is found in veins.

Filtration of serum lipids and other partially filterable substances through arteries results in their retention and deposition in the tissues of the artery wall. Serum lipids, however, are able to filter through the walls of veins without or with only very slight intramural deposition.

Wrinch, Dorothy. (*Dept. of Phys., Smith Coll., Northampton, Mass.*): MOLECULES OF THE INSULIN STRUCTURE. Science *116*:562-64, November 21, 1952.

The author discusses the structure of the insulin moleculeon the basis of crystallographic and molecular weight data.

Yu, Paul N. G. (*Chest Lab. and the Heart Sta. of the Dept. of Med., Univ. of Rochester Sch. of Med. and Dent., and the Med. Clinics of Strong Mem. and Roches-*

ter Mun. Hosps., Rochester, N. Y.): THE ELECTROCARDIOGRAPHIC CHANGES ASSOCIATED WITH HYPERCALCEMIA AND HYPOCALCEMIA. Am. J. M. Sc. *224*: 413-23, October 1952.

The author describes the electrocardiographic changes in 2 cases of hypercalcemia and 10 cases with hypocalcemia.

With hypercalcemia the characteristic findings are shortening of the ST segment and the QT interval. With hypocalcemia the ST segment and the QT interval are prolonged. These changes are always seen when the serum calcuim level increases to 13 mg. per 100 cc. (6.5 mEq/L) or decreases to 6 mg. per 100 cc. (3.0 mEq/L). The changes in the duration of the ST segment and QT interval may serve as an important adjunct in the qualitative diagnosis of hypercalcemia or hypocalcemia in the obsence of other electrolyte disturbances.

There is a significant correlation between the serum calcium level and both the ST segment and the corrected QT interval.

Disturbances in serum calcium levels and other conditions producing similar changes, such as serum potassium abnormalities, digitalis and quinidine therapy, and acute pericarditis, may be distinguished by the fact that serum calcium abnormalities affect only the duration of the QT and ST intervals without associated deviations of the ST segment, T wave and V wave changes, and abnormalities in the QRS complex and PR interval.

Zarrow, M. X.; Denison, M. E.; Rosenberg, B.; Mann, D. E., Jr.; and Neher, G. M. (*Dept. of Biol. Sci., Purdue Univ., Lafayette, Ind.*): EFFECT OF INSULIN AND EPINEPHRINE ON THE EOSINOPHIL AND BLOOD GLUCOSE LEVELS IN SHEEP; LACK OF DIURNAL RHYTHM. Am. J. Physiol. *171*:636-40, December 1952.

Studies on blood glucose and eosinophil levels indicate a lack of diurnal rhythm in the sheep. Treatment with insulin or epinephrine produces the expected effects on the blood sugar and a definite eosinopenia. The failure to find a diurnal rhythm or to obtain any response with the stimulus of handling is added evidence for the theory that sheep possess a relative deficiency in the pituitary-adrenal mechanism.

Zimmerman, Hyman E.; Walsh, John R.; Johnson, Richard B.; and Humoller, Fred. (*Dept. of Med. and Res. Lab., Vet. Admin. Hosp., Omaha, Neb.*): INEFFECTIVENESS OF DESOXYCORTICOSTERONE ACETATE IN INHIBITING THE DEPRESSION OF BLOOD EOSINOPHILS IN PATIENTS RECEIVING INSULIN-SHOCK THERAPY. Am. J. Med. *12*:610, May 1952.

Total eosinophil counts were obtained initially and five hours after the administration of insulin in a group of psychiatric patients receiving insulin shock treatment. The results obtained in patients pretreated with desoxycorticosterone were compared with those in patients not receiving this steroid. A profound drop ranging from 70 to 90 per cent of the control value was observed in the latter patients. Although a wide variation in the resting level was noted from day to day and from patient to patient, the insulin-induced eosinopenia was seen in all. The intramuscular administration of desoxycorticosterone, either as a single dose of 10 mg. twelve hours before the insulin was given or as a daily dose for varying periods up to fourteen days, was found to be completely ineffective in preventing the eosinopenia. The authors conclude that the inability of DCA to inhibit the eosinopenia that develops in patients receiving insulin shock therapy may mean that contrary to results reported in rats, this steroid fails to inhibit the release of ACTH in humans.

EDITORIALS

*DIABETES CONTROL**

Active, progressive, and uncontrolled diabetes results in premature widespread vascular degeneration. The question of the role which insulin deficiency plays in the tragedy of arterial deterioration may well lead to solving the most important pathological enigma of the present day, namely, arteriosclerosis. It is logical to assume that the earlier the diabetes is identified and an adequate program of management established, the less likelihood for complications to develop. There is wide-spread agreement that satisfactory control is based on diet, insulin, and exercise.

During the last 25 years the science of nutrition has made great strides. The danger of overweight for young and old is now recognized. By long continued overeating the potential diabetic may cause exhaustion of the pancreas and frank diabetes with the ordinary clinical symptoms. Metabolic exhaustion has been demonstrated experimentally to be an important precipitating factor. Prolonged fatigue, likewise, predisposes to vascular complications in the older patient.

Pancreatic exhaustion reduces the amount of available insulin in the pancreas. Insulin deficiency, relative or absolute, is the basic cause of diabetes. It would appear that the younger the patient the greater the loss of insulin production by the pancreas. Wrenshall and his co-workers found that insulin which could be extracted from the pancreas of diabetics averaged less than 40 per cent that obtained from the pancreas in normal individuals. In childhood diabetes it is less than 10 per cent of the amount extractable from the adult diabetic pancreas.

Continual overeating tends to prolonged increase in the level of the blood sugar. This stimulates the pancreas to make more insulin to meet the increased demand. Temporary exhaustion of the beta cells of the islets may occur. From observations on alloxan diabetes in animals, the early evidences of exhaustion, increase in cell size, cloudy swelling, changes in cell structure, if not too long in duration, may return to the normal healthy state provided the insult to the insulin-producing cells has not been too long in existence. Prolonged fatigue aggravates the strain on the beta cells. The homeostatic mechanisms of the body carry on most satisfactorily with a minimum of strain on specific cell functions when overloading and exhaustion are avoided.

What constitutes control of diabetes? What is the dividing line between satisfactory metabolic balance and the early defections which if not controlled would lead to serious complications? The answer to this inquiry is important. The criteria of adequate control are not generally agreed upon. The two items about which no agreement has been reached are blood sugar levels and sugar in the urine. Some men with expert knowledge and wide experience discount the importance of high blood sugars and glycosuria in the absence of other findings indicative of marked metabolic dysfunction.

For practical purposes it would be exceedingly helpful if definite criteria could be established indicative of the limits of the excursion of the blood sugar level, the duration of the elevation and the amount and time interval of the duration of glycosuria. Obviously, and yet again it might not be so direct as it sounds, a blood sugar level within normal limits and the absence of urinary sugar indicates satisfactory control. Yet, thinking just a little further, it must be admitted that when the diabetic patient becomes the victim of various ailments, infectious processes, and what not, he may be in poor metabolic balance and still have a blood sugar level within normal.

*Presented at the Postgraduate Course given by the American Diabetes Association in Toronto, January 19, 20, and 21, 1953.

Industry, labor, and the general public look to our Association for enlightenment. If we find disagreement among ourselves it stands, whether justified or not, as an accusation. The lay public interprets our dilemma in an unfavorable light. Regardless of the difference in origin of the metabolic defect, maintenance of nutritional balance with complete utilization of foodstuffs represents the ideal control. Emphasis should be placed on how much of the diet is utilized. Determinations of excess blood and urinary sugar are helpful in estimating the efficiency of the metabolic fire.

Criteria of satisfactory control are the same from infancy through the years to old age. The margins of safety, however, vary with age. The child diabetic is known to be very susceptible to acidosis. His margin of metabolic reserve frequently is limited. It is practically impossible to hold the growing youngster in nutritional balance without some degree of glycosuria at times, unless he is subjected to frequent unpleasant episodes of insulin shock. The common practice is to maintain the growing child on a generous diet including the essential building materials for body growth and organ function, plus the exceedingly important factor of satisfactory emotional maturation. To a generous extent the management of diabetes is a family problem, especially when the patient is a child.

In calculating the total carbohydrate available in the diet and compared with the amount of loss in the urine in 24 hours, a helpful estimate is obtained. Long continued elevation of the blood sugar and sustained loss through the kidneys represents inadequate control. Long continued glycosuria without ultimate kidney damage rarely occurs.

The fatigue element has not been sufficiently stressed. The experiments of Lukens and co-workers have demonstrated that long continued overloading of the pancreas in laboratory animals leads to anatomical changes. These suggest functional exhaustion in the early stages. Pancreatic exhaustion produced by carbohydrate overloading, or toxic chemicals such as alloxan, produce a state of exhaustion. The same sequence of events probably takes place within the human body. Pancreatic exhaustion is a commonly occurring condition in the precipitation of diabetes.

When the basic initial condition favoring the onset of the diabetic state is thus visualized, it offers a working hypothesis for control. If Cannon's views on homeostasis are acceptable, the normal values for blood metabolites should represent the most favorable blood and tissue concentrations for body function. The further away the deviation from the normal pattern, the more the lack of adequate control.

It is understandable, therefore, why the most advanced lesions of diabetes are commonly found in those patients with inadequate control for long periods of time. Granted the exact mechanism of vascular deterioration is not as yet understood. The fact remains that the most prominent degrees of arterial degeneration have been identified in long standing diabetes. Some years ago when the high fat diets were tried, the clogging of blood vessels in the lower extremities with large fat globules was a common finding at autopsy. We are indebted to Root, Marble, and their colleagues for detailed studies on the relationship between various degrees of blood sugar control and the occurrence of degenerative lesions in young diabetics. Some observations have been offered which at first glance might tend to contradict their conclusions. It should be kept in mind that among nondiabetics, the hereditary factor of tissue stamina and predisposition to degenerative lesions exists. With this qualification the additional strain of poor metabolic control augments and accelerates blood vessel breakdown. Individuals with a strong hereditary background possessed of a rugged vascular system will be less likely to show premature vascular deterioration if, when diabetic, the blood sugar level is maintained within homeostatic balance.

An adequate amount of insulin is a requirement equally important to diet in control of diabetes. Sherrill has illustrated the role which insulin plays in maintaining a satisfactory nutritional balance in each body cell. As the body mass increases there is a correspondingly inadequate amount of insulin for each unit of body weight. Therefore, if a low calorie diet reduces the body mass, there is a relatively greater amount of insulin for each cell. This is seen clinically when exogenous insulin is frequently no longer necessary when the obese patient rids himself of excess body mass.

Theoretically, the diabetic will not lose his control if there is always a moderate amount of food available by eating small quantities at frequent intervals; and if the estimated insulin deficiency of his pancreas is compensated for by a continuing and frequent administration of exogenous insulin. Ketosis and reactions from insulin over dosage are preventable and for the most part inexcusable.

Exercise is the third requirement for diabetes control. Muscular activity even for the older patients conditions organ function. It has a tonic effect on the circulation, digestion, liver function, and elimination of the body

wastes. The exact part exercise plays in protecting or predisposing to excess wear and tear on body tissues, especially of the vascular system, is not known. The sedentary individual who is continually feeding into his blood stream a concentrated caloric flow must, thereby, expose the vascular walls to greater strain than if the blood stream is speeded up by physical activity. Exercise may exert an influence as a catalyst by shortening the time period during which a high caloric concentrate is bathing the vascular walls. The sense of well being experienced following exercise may be the result of speeding up the blood stream, improving the tonicity of the vascular walls and shortening the danger period of exposure to metabolic concentrates which are commonly found in the walls of diseased blood vessels.

Diet, insulin, and exercise with the avoidance of prolonged exhaustion are the requirements upon which diabetes control is established. The exact level of the blood sugar is but one measure of control. For a physician interested in maintaining control of the diabetic state, the available evidence emphasizes the importance of maintaining the level of the blood sugar not over 200 mg. for any prolonged period of time. Granted many individuals may carry on apparently in satisfactory fashion with blood sugar levels over 400 mg. and more or less constant glycosuria for a variable period of time. Acceptance of such distortion of normal body chemistry as a condition compatible with well being is a dangerous practice. There are still many angles of the diabetic problem for which no answers are yet available. Nevertheless, the more clearly the metabolites and electrolytes of the blood fall within the accepted normal range, the closer will the diabetic come to satisfactory control.

EDWARD L. BORTZ, M.D.

DIABETIC RETINOPATHY.

The characteristic vascular lesion of diabetic retinopathy consists of the presence of great numbers of minute saccular aneurysms in the retinal capillaries. Hemorrhages and exudates commonly surround the aneurysms, indicating that these are loci of weakness in the vascular wall. The aneurysms are often hyalinized. Capillary aneurysms in the retina are also seen in a variety of other retinal lesions involving tissue damage, venous occlusion, etc. but in these conditions the aneurysms are mainly fusiform or varicose, while in the diabetic they are mainly saccular.

The retinal lesions of the diabetic are closely related to the renal lesions described by Kimmelstiel and Wilson. The latter are often associated with capillary aneurysms in the kidney glomerulus, and the typical globular hyalin, glomerular nodule of Kimmelstiel and Wilson may, in fact, be a hyalinized saccular capillary aneurysm. Kimmelstiel[1] believes that the hyaline material in the glomerular lesion is laid down outside the capillary basement membrane, while I have suggested[2] that the hyalinization occurs inside the aneurysmal sac in the retina, but it is agreed that the retinal and renal lesions are joint manifestations of the same vascular disease. Neither these retinal nor these renal lesions, characteristic of the diabetic, are direct consequences of atherosclerosis or malignant hypertension. They are almost never seen in atherosclerotic or hypertensive nondiabetics and may occur in diabetics in the absence of both athero- and arteriolosclerosis. Patients with diabetic retinopathy and nephropathy commonly show increased capillary fragility suggesting the presence of a generalized capillary disease, but microaneurysms have so far not been demonstrated in significant numbers in organs other than retina and kidney.

The characteristic capillary lesion is most frequently seen in diabetics of long standing, but it is not directly related to the severity of the diabetes in terms of insulin requirement. Many patients show a decline in insulin requirement associated with the onset of the retinopathy. The relative frequency of episodes of acidosis in patients with and without retinopathy is disputed. Zubrode, Eversole and Dana[3] found a lower frequency of acidosis in adult diabetics with than without retinopathy and nephropathy. Wilson, Root and Marble[4] found a higher frequency of acidosis in juvenile diabetics with than without retinopathy. In extremely rare instances, retinopathy or nephropathy morphologically identical with those of the diabetic have been found in nondiabetics.

Rich, Berthrong and Bennett[5] discovered that renal lesions resembling those of the Kimmelstiel-Wilson nephropathy could be produced in rabbits in a period of 2 to 3 weeks by the administration of 7.5 mg. of cortisone in daily intramuscular injections. Rich[6] found typical Kimmelstiel-Wilson nephropathy in a nondiabetic patient who had been subjected to very prolonged corticotrophin (ACTH) therapy. Naquin[7] has noted the appearance of retinal capillary aneurysms in nondiabetics under corticotropin treatment. Friedenwald and Becker have found that alloxan diabetes in rabbits predisposes these animals to the capillary lesions elicited by cortisone and corticotropin. They have,[8] therefore, suggested that the retinopthy and nephropathy of the diabetic may be the consequence of an increased secretion of cortisone

(or related substances) by the adrenals of these patients.

Clinical estimates of adrenal activity with respect to glucocorticoids are extremely tenuous. Thorn,[9] using as an index the fall in eosinophile count following corticotropin administration, concluded that about half of all diabetics tested showed deficient adrenal function. Thorn's patients were unclassified with respect to the presence or absence of retinopathy. Hoover, Becker and Winter, in a similar study, found that all the diabetics exhibiting adrenal hypofunction by this test were free of retinopathy. Within the limits of reliability of this test, diabetics with retinopthy exhibit more adrenal activity than the average diabetic without retinopathy. Shadaksharappa[10] studied the urinary steroid excretion in a small group of diabetics. Those with and without retinopathy showed diminished output of ketosteroids, but diabetics with retinopathy excreted more oxysteroids than did those without retinopathy.

Pregnancy is normally associated with increased adrenal function and might be expected, therefore, to exacerbate diabetic retinopathy. This has been found to be the case by Lawrence (1948),[11] and Becker (1952).[12] Green (1951)[13] reported the disappearance of retionopathy in one diabetic patient following surgical removal of the adrenals. A spontaneous disappearance of the retinopathy has been recorded in a diabetic who developed Simmonds' disease.[14] Saskin[15] and coworkers have reported improvement in the retinopathy of some diabetics treated with testosterone. The administration of testosterone has been shown to produce atrophy of the hypophysis and diminish adrenal activity in animals.[16] It has been used effectively in some cases in the treatment of Cushing's disease.[17] Many of the diabetics treated with testosterone show diminished daily insulin requirement as would be expected if they were experiencing diminished adrenal activity.

The clinical evidence summarized above is tenuous and indirect. The best that can be said about it is that, so far, no clinical findings contradict the hypothesis of Becker and Friedenwald of relative adrenal hyperfunction in diabetics with retinopathy. In the experimental animal, the interaction of alloxan diabetes and cortisone or corticotropin in the production of retinal and renal capillary lesions is unequivocal. What, then, are the possible metabolic and biochemical pathways of this interaction? Exploration of this problem has just been begun but some possible clues may be enumerated.

Both insulin and cortisone seem to be involved in mucoid metabolism. Jacobs[18] found that the glucosamine fraction of plasma mucoid rose and fell with the plasma glucose of diabetics in response to insulin withdrawal and administration. Glick[19] finds that the hyaluronidase inhibitor of the plasma increases after administration of cortisone, and diminishes after adrenalectomy. Layton[20] found that cortisone inhibited the synthesis of mucoid sulfates. McManus[21] has suggested on morphologic grounds that the retinal and renal capillary lesion of the diabetic might be the result of a disturbance in mucoid metabolism. It seems possible that some defect in the basement membrane of the capillary may be the immediate cause of the aneurysms.

Both pancreas and adrenal dysfunction have large effects on the utilization of several of the B vitamins. Many diabetics show evidence of deficiency in some B factors and some B deficiencies can be demonstrated in alloxan diabetic animals. The association of diabetic neuritis with diabetic retinopathy is by no means infrequent. The vitamin deficiency of the diabetic probably is not generally to be accounted for by his restricted diet, but it may be noted that a severe increase in diabetic retinopathy was observed in Denmark[22] during the period of war time food restriction. The reason for the apparently enhanced vitamin requirement of the diabetic is obscure, but insulin is required for the formation of high energy phosphate compounds, and hence indirectly for the conversion of most of the B vitamins into their phosphorylated functionally active forms. Even the parenteral administration of insulin with adequate control of the blood sugar level may not fully replace the diabetic's insulin deficiency in the portal circulation.

Deficiencies of pantothenic acid, pyridoxine, and thiamine have each been shown in experimental animals to cause depletion of lipoids in the adrenal cortex. The interpretation of these findings is equivocal since lipoid depletion in the adrenal may result from stress, that is adrenal hyperactivity, or from an incapacity to synthesize the adrenal lipoids. In regard to these B vitamin deficiencies, a choice between these two possible interpretations cannot in each case be made on the basis of currently available data. However, it has been shown that deficiency of pantothenic acid is associated with adrenal hypofunction.[23] Moreover, the body can synthesize its steroids from acetate and the biochemical production of active acetyl groups requires the presence of coenzyme A of which pantothenic acid is an integral part.

As was noted above, some diabetics without retinopathy show adrenal insufficiency in terms of a defective eosinopenic response to corticotropin. Winter[24] has recently tested the possibility that this defective response might be due to pantothenic acid deficiency, and has

found that the response in these patients becomes normal after administration of pantothenic acid alone or with pyridoxin. The pantothenic acid deficiency in these cases appears to be quite marginal, and is not associated with a grossly deficient capacity in acetylation.[25] In experimental animals on a pantothenic acid deficient diet, it has been found that diminished adrenal function develops before gross evidence of insufficiency in other organs.[26]

The relation of adrenal function to vitamin B_{12} is very different from the pantothenate-adrenal interrelation. B_{12} deficiency in contrast to pantothenate deficiency has not been shown to be associated with adrenal lipoid depletion or adrenal hypofunction. Symptoms of B_{12} deficiency are markedly exacerbated by cortisone[27] and the turnover of this vitamin is greatly accelerated in adrenal hyperfunction. Chow and Becker found that cortisone treated animals and humans excrete far larger fractions of a test dose of B_{12} than do normals. Some of the symptoms of cortisone intoxication, for instance, thymus atrophy,[28] are reversed by administration of B_{12}. Chow and Becker[29] have tested the capacity of diabetics with and without retinopathy to retain a test dose of B_{12}. They found that diabetics without retinopathy excreted in their urine a smaller fraction of the test dose than did normals. They interpreted this as indicating B_{12} deficiency in this group of patients.

Diabetics with retinopathy excreted as much or more of the test dose than do normals. This might indicate that these patients were saturated with B_{12} or that they were unable to retain the test dose because of adrenal hyperfunction. To test this, these patients were treated with testosterone and retested for B_{12} excretion. In every case greater retention of B_{12} was found after testosterone than before. The increased retention was most marked in those patients who showed increased insulin sensitivity after the testosterone, that is, evidence of diminished adrenal function.

Becker, Winter and Friedenwald then tested the influence of B_{12} deficiency in rabbits on the renal lesions produced by cortisone. Nondiabetic animals on a B_{12} deficient diet, given 7.5 mg. of cortisone daily for two weeks, showed a much higher incidence of renal lesions resembling the Kimmelstiel-Wilson nephropathy than did animals on a normal diet containing aureomycin and vitamin B_{12} subjected to the same cortisone treatment. The lesions were, in fact, more severe and abundant than those produced in alloxan diabetic animals on a B_{12} supplemented diet given the same cortisone treatment. It would appear, therefore, that one of the convergent metabolic pathways leading to the production of the vascular lesion may be B_{12} deficiency induced by diabetes and exacerbated by adrenal hyperfunction.

In general, the diabetic shows an increase in plasma lipids. Lipemia is common in alloxan diabetic rabbits. Increased blood lipids can also be produced by cortisone and this effect is found in experimental rabbits. In rats, on the other hand, lipemia is not readily elicited either by alloxan diabetes or by cortisone administration, and this species does not develop retinal or renal capillary aneurysms under the experimental conditions that produce these lesions in rabbits. It would seem possible, therefore, that a disturbance of the fat metabloism may be related to diabetic retinopathy and nephropathy. A recent issue of DIABETES was devoted to reports from several clinics on the blood lipids of diabetics with and without retinopathy.[30]

The possible clues as to the locus of metabolic interaction between the diabetic state and adrenal hyperfunction lead in many diverging directions. The brief list enumerated above by no means covers all of the possibilities. Somewhere in this perplexing nexus the immediate cause of the retinopathy may one day be found. Root has said that it makes no sense to consider diabetes as unrelated to pancreatic dysfunction. With this, I am in full agreement, but it would be fatuous to assume that the whole complex of symptoms, complications and sequelae of diabetes are simply and directly related to hypo-insulinism.

JONAS S. FRIEDENWALD, M.D.

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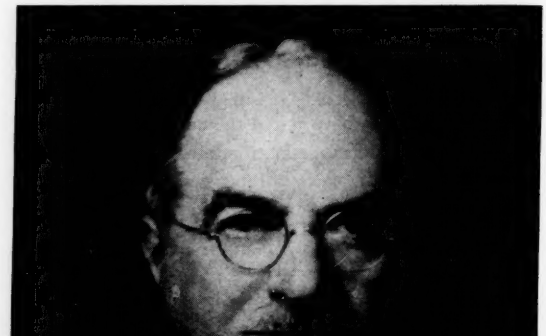
LOUIS I. DUBLIN, MEDICAL STATISTICIAN

News of the retirement of Louis I. Dublin, Ph.D., from his post as Statistician and Second Vice President of the Metropolitan Life Insurance Company, recalls not only his distinguished personal career but also the growing significance of studies of statistics in relation to medical problems. Progress in medicine long depended chiefly on clinical observation. In recent generations, great advances have been aided by laboratory investigation. The increasing recognition of the value of medical statistics is in great measure due to Doctor Dublin's work.



Louis I. Dublin

Doctor Dublin organized the Statistical Bureau of the Metropolitan Life in 1911, and was its chief until his retirement at the close of 1952 when he completed 44 years service with that company. He continually focused attention on the social and economic losses suffered by the country as a result of preventable sickness and pre-

mature death. Under his farsighted leadership many outstanding studies have been made on public health, mortality, morbidity, longevity, and population problems. The monthly *Statistical Bulletin,* which he edited, made these valuable facts available to the public.

Since its beginning in January, 1920, the *Statistical Bulletin* has included many articles on diabetes, the first appearing in the July, 1920 issue. Annual mortality statistics on diabetes among Metropolitan Life industrial policy holders first appeared in the *Bulletin* for January, 1922; this included figures for that period from 1911 to 1921. Monthly death rates from the disease have been published regularly since 1923.

Among Doctor Dublin's 660 publications including books, papers, and addresses, there were 19 which dealt specifically with diabetes. The earliest paper dealt with mortality statistics of diabetes and comparative incidence of the disease in the general population. His last publication, which appeared in DIABETES, May-June, 1952, dealt with mortality from the disease throughout the world. Statistics on diabetes constituted a part of a great number of his other publications.

Born in Lithuania in 1882, Doctor Dublin received the B.S. degree from the City College of New York in 1901, and the degree of Ph.D. from Columbia University in 1904. After several years of teaching mathematics and biology in New York, he joined the Metropolitan Life Insurance Company in 1909 and was appointed Statistician in 1911; he became Third Vice President in 1941 and Second Vice President in 1944. He lectured on vital statistics at Yale University from 1917-1923. He has been active in numerous health and welfare organizations. He was President of the American Public Health Association, 1931-32, and served as Treasurer of that organization for 25 years. In 1924, he served as President of the American Statistical Association. He served also as President of the Population Association, and for 9 years was Chairman of the Board of the American Museum of Health.

DIABETES adds its congratulations to Doctor Dublin at this point in his outstanding career and is happy to hear of his continued activity in the field of public health as consultant to the Institute of Life Insurance and the Health Information Foundation, as well as by his uninterrupted association with many voluntary health organizations.

Diabetes Mortality and Education

The diabetic mortality is rising at an alarming rate. This may indicate a deficiency on the part of the lay public to appreciate the value of modern medical procedures, or to appreciate the significance of their early symptoms. This requires a dual attack. On the one hand it is essential that the American Diabetes Association further the education of the laity, and on the other hand that the medical profession be constantly reminded of the more recent advancements in the practical treatment of the diabetic patient. Towards this end the American Diabetes Association should have Committees to deal with both aspects of the problem.

Associated with the problem of continual education of the laity and postgraduate training of the physician, is the advisability of the formation of local organizations concerning themselves with these questions. Such organizations now exist in a number of cities. It should be one of the purposes of the American Diabetes Association to encourage the formation and integrate the activities of the various local diabetes organizations. This implies the necessity for setting up a central office which can act as a clearing house for all problems pertaining to diabetes, so that any group or individual can obtain authentic information concerning diabetes. Thus, it would be possible to sponsor lectures and demonstrations for the laity at various times throughout the year in various communities. For example, the establishment of demonstrations and the appointment of a group of lecturers would simplify and expedite such demonstrations in various cities; the same lecturers or demonstrations being employed throughout. Likewise through the offices of the American Diabetes Association, lecturers on diabetes for the medical profession can be recommended to local organizations and demonstrations for the medical profession can be sent out to such groups. It is our hope that in the not too distant future the financial situation of the American Diabetes Association will make it possible for us to have a full-time paid executive secretary whose duties will revolve around such a program.

From *The President's Address,* by Cecil Striker, M.D., in Proceedings of the American Diabetes Association *1*:25-26, 1941

GRAHAM LUSK

And His Contributions to the Science of Nutrition

Cecil Striker, M.D. CINCINNATI, OHIO

"If there be any one book having a wider penetrating influence on medical research in this country than Lusk's on the science of nutrition I do not know it. If there be, to date, by the pen of any other man in any language, a better discussion of the whole scope of the science of nutrition, I have not seen it." This statement of Professor A. J. Carlson in regard to "The Elements of the Science of Nutrition," by Graham Lusk, was among the many tributes to his stature as a scientist.

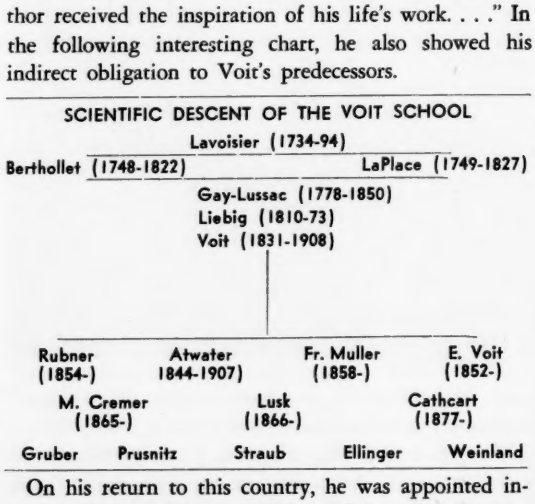
Lusk, who lived from 1866 to 1932, published over 150 scientific papers and either wrote or contributed to 12 scientific books. The most important of them was the text named above, which went through four editions. He thus exerted a great influence upon scientific thinking and on the development of a new phase of physiology in the United States, in the Western hemisphere and in the entire world. This phase of physiology concerned itself with nutrition and has developed into the science of metabolism.

Lusk came from superior stock. His ancestors were early settlers in New England and remained in Connecticut for many generations. His father was a practitioner of medicine who recognized the value of a sound scientific training, having studied chemistry and physiology in Europe for several years before entering the practice of medicine. He was noted particularly in the field of obstetrics; but always kept his physiologic training as the basis for his many scientific papers and books, his practice and his teaching, first at Long Island College, later as a lecturer at Harvard, and as professor of obstetrics at Bellevue Hospital Medical College.

Graham Lusk was born in Bridgeport, Connecticut on February 15, 1866 and shortly thereafter the family moved to New York for permanent residence. Lusk, stimulated by his father's keen scientific approach, devoted himself to a scientific career. When he was sixteen, he spent a year traveling in Europe, after which he studied chemistry at the School of Mines at Columbia University, from which he received a degree in 1887. On account of an increasing deafness, his father persuaded him to give up the idea of the practice of medicine and he went abroad intending to study chemistry and physiology under Hoppe-Seyler. In Munich he visited a friend of his father who gave him a note of introduction to Carl von Voit. Voit's influence on Lusk was a powerful one and changed the entire pattern of his life. He worked with Voit for several years and received a Ph.D. from Munich in 1891. His work in Voit's laboratory, starting with a problem on diabetes, initiated a long series of intensive studies on nitrogen equilibrium, calorimetry, the D-N ratio, and the fate of amino acids in the body.

Lusk dedicated his famous book "To the memory of Carl von Voit, master and friend, from whom the author received the inspiration of his life's work. . . ." In the following interesting chart, he also showed his indirect obligation to Voit's predecessors.

SCIENTIFIC DESCENT OF THE VOIT SCHOOL



On his return to this country, he was appointed instructor in physiology at Yale and in 1895 he was made professor. In 1898, he accepted the chair of physiology at New York University and Bellevue Medical

College. He remained there until 1909 when he became professor of physiology at Cornell University Medical College in New York City, a post which he held until a few days before his death on July 18, 1932.

At Yale, Lusk began his work on phlorizin diabetes, which led to a prolonged investigation of the sources of glucose in the body. When he came to New York, he had the opportunity of extending his observations to the metabolism in human diabetes. In both conditions, he found a definite ratio between the dextrose formed in the organism and the protein metabolized as represented by the nitrogen excretion. By means of this D-N ratio he studied various amino acids as sources of carbohydrate.

In 1912, he became the scientific director of the Russell Sage Institute of Pathology. A respiration calorimeter for human subjects was contructed near the medical wards of Bellevue Hospital and during the course of the next twenty years, he was able to plan experiments on dogs and supplement them by means of observations on human subjects. These very intricate and prolonged experiments were the basis for all of the calculations on the extensive work on severe diabetes that was being carried out throughout the country before the discovery of insulin. To him and his group goes the credit for laying the background for the fundamental metabolic changes occurring in diabetes; and it is fair to say that the improvement in the understanding of the metabolic changes in diabetes since the discovery of insulin could not have taken place without such fundamental work as was done by Doctor Lusk.

Perhaps the chief service of Graham Lusk was his constant readiness to help younger men. There were hundreds of them who went to him with their problems, and they always received his aid and inspiration. Not only the men who worked in his own laboratory, but those from far distant parts of this country and Europe are indebted to him for much of the best parts of their publications.

Scientific meetings were always a particular source of his pleasure and he played an important part in such gatherings. The original idea for The Harvey Society arose in the mind of Graham Lusk and received the immediate support of others. The first meeting was held in Doctor Lusk's home, in the same room where The Society for Experimental Biology and Medicine was founded by him two years previously. He was an active or honorary member of physiological and scientific societies in many countries and during the First World War he served on The Inter-Allied Scientific Food Commission, as one of the representatives of this country.

Following a report on American medical education in the first decade of this century by Dr. Abraham Flexner, Doctor Lusk recognized that the methods of science must be applied in the clinic, as well as elsewhere in the medical school, if medicine was to advance. He quickly enlarged his facilities for physiological investigation at Cornell University Medical School and increased the opportunities for these investigations to be applied to clinical medicine. He enlisted the cooperation of his clinical colleagues in research on metabolism of sick persons and gave opportunity to many clinicians to participate in these investigations. The men who worked in this early period included Howland, DuBois, Aub, Peters, McCann, Barr, Richardson, among many others. Everlasting credit should be given to him for improving the quality of preclinical training in the medical schools.

As a person he had a great cheerfulness, a keen sense of humor and a genius for friendship. He was a most gracious host in his home, which became the mecca of visiting scientists, and on one occasion he entertained the entire International Physiological Congress. In spite of his deafness, he was a good conversationalist and an effective public speaker. He was a tireless worker and had a retentive memory. A staunch friend, he had no patience with insincerity.

Lusk was one of the great figures in American medicine contributing to and developing a new science, making great strides in the improvement of medical education, assisting in the development of young scientists, and fighting always for the good of the scientific world.

Among many famous students, he has left one who has been able to carry on his activities and do much for the perpetuation and further development of the work in which he pioneered. That one is Professor Eugene F. DuBois. His many scholarly and intimate papers on Graham Lusk have been the inspiration and the source of the material here presented. The writer gratefully acknowledges his debt to Doctor DuBois.

REFERENCES

Eugene F. DuBois: Graham Lusk. Science, 76: 1962, August 5, 1932.

Eugene F. DuBois: A Tribute to Graham Lusk. Jour. Am. Diet. Assn., 9:5, Jan. 1933.

Eugene F. DuBois: Biographical memoir of Graham Lusk. National Academy of Sciences. Vol. 21, 1940.

BOOK REVIEWS

NUTRITION AND DIET IN HEALTH AND DISEASE. *By James S. McLester, M.D., Professor of Medicine Emeritus, University of Alabama, and William J. Darby, M.D., Ph.D., Professor of Biochemistry and Director of the Division of Nutrition, Vanderbilt University. Cloth. $10.00. Pp. 710; illustrated; 6th edition. Philadelphia, W. B. Saunders Company, 1952.*

This text book which first appeared a quarter of a century ago has been revised for the sixth edition with the collaboration of a junior author who has undertaken responsibility for the first part, dealing with nutrition in health. This section deals with the biochemical and physiological problems of food and its utilization including detailed information regarding the vitamins, the protein problem, and inorganic nutrients. Information helpful to the physician is given in regard to many food products. The dietary requirements of normal individuals are presented including special consideration of infants, children of school age, aged persons, and pregnant women.

The senior author has devoted special attention to the second part, dealing with nutrition and disease. Approximately 38 pages have been devoted to diabetes mellitus, including 5 pages about insulin. The method of planning diabetic diets with food exchange lists prepared by the American Diabetes Association and the American Dietetic Association, in co-operation with the Diabetes Branch of the U. S. Public Health Service is presented. Emphasis is placed on accuracy of dietary control with full consideration of the psychological factors affecting the interests and desires of the patient.

The excellent attention given to the dietary problems in diabetes is similarly displayed in the sections dealing with deficiency diseases, gout, obesity, and also diseases of the digestive system. An effort has been made further to include some dietary information regarding almost every disease which may be encountered. This leads to the inclusion of much material which would have been better omitted. Examples are such statements as "Multiple sclerosis has been attributed to vitamin deficiency, but the evidence presented has been discarded." "Parkinson's syndrome has been treated with pyredoxine . . . but many failures also have been reported."

In the appendix one finds 76 pages of tables giving a variety of information including dietary standards, composition of foods and nutrients in household quantities.

The book should continue to prove valuable to both medical students and practicing physicians.

ENDOCRINE TREATMENT IN GENERAL PRACTICE, edited by Max R. Goldzieher, M.D. and Joseph W. Goldzieher, M.D., Cloth, Price $8.00, Pp. 474, 19 illustrations, Springer Publishing Company, Inc., New York, 1953.

This book, written particularly for the general practitioner, presents the diagnosis and treatment of endocrine diseases and also the treatment of non-endocrine diseases with various hormones especially corticotropin and cortisone. Edited by the Goldziehers, father and son, it is the product of the editors' collaboration with 19 other contributors in various fields of medicine.

Organization of the contents is based on the localization of the presenting symptoms and the types of metabolic disturbances, rather than subdivision of the book according to the individual endocrine glands. The editors have attempted in this organization and in their discussions to create, not a textbook, but a practical handbook for the busy medical practitioner who has found it difficult to keep up with recent advances in endocrinology. This has been accomplished by the elimination of all background material, controversial discussion, and references. The contributors have simply summarized their opinions and experiences in their own individual fields.

Many chapters are particularly well written. The common endocrine disorders of infancy and childhood are clearly outlined. The chapter on carbohydrate and fat metabolism written by Dr. George E. Anderson presents a practical discussion on diabetes mellitus including excellent dietary material. Other outstanding chapters on endocrine subjects include: water and electrolyte metabolism, male infertility, female hypogonadism, virilism, disorders of menstrual function and menopausal syndrome.

The several chapters describing the effects of endocrine diseases on different organ systems in the body help to make this book more effective as a reference source, but there is much repetition of material covered elsewhere, especially in regard to treatment. The three chapters describing endocrine therapy of diseases of the skin, eyes and neoplastic diseases should be valuable. The conveniently arranged list of the various types of hormone preparations currently available, appearing at the end of the book, should also be helpful.

The reviewer's chief criticism is the recommendation by certain contributors of the use of endocrine products in the treatment of non-endocrine diseases. Examples include the use of testosterone for senescense, thyroid and pituitary extracts for obesity, and testosterone for either functional symptoms or psychogenic impotency of the middle aged man who has no proved androgen deficiency. According to many and perhaps most authorities in endocrinology, these substances have not been shown to be as effective as appropriate psychiatric therapy and placebos. Other measures pertaining to endocrine disease such as the treatment of Cushing's syndrome due to adrenal hyperplasia by the use of cortisone rather than by partial or total adrenalectomy, and the use of the glucose tolerance test rather than a prolonged fast in the diagnosis of organic hypoglycemia, would not be accepted by authorities who have had the most experience in these particular fields.

In the opinion of this reviewer, the book can be definitely recommended and will be a valuable aid to the general practitioner.

DISEASES OF METABOLISM, Detailed Methods of Diagnosis and Treatment, edited by Garfield G. Duncan, M.D., Director of Medical Division, Pennsylvania Hospital and Clinical Professor of Medicine, Jefferson Medical College, Philadelphia, Cloth, $15.00, Pp. 1179, illustrated, 3rd edition, Philadelphia, W. B. Saunders Company, 1952.

The editor has had the assistance of 20 distinguished authorities in writing a textbook which includes not only information about the diseases of metabolism but also an excellent presentation of normal metabolic processes and problems in endocrinology which border on the field of metabolism.

The section on diabetes mellitus has been written by the editor himself, with sections on diabetes in childhood and melituria contributed by Priscilla White and Cantarow. The information concerning diabetes, based on the authors' extensive experience, is authoritative and well written. In the section concerning dietary treatment, the food exchange system and the ADA diets are recommended.

Soskin and Levine have contributed the valuable section on carbohydrate metabolism. This includes an exposition of the controversial problems concerned with gluconeogenesis, the enzymatic machinery of metabolism, the mode of action of insulin, and the influence of other hormones. Other subjects which deserve special commendation include water balance, written by Peters, vitamins by Spies and Butt, and obesity by Evans.

The book can be highly recommended because it successfully presents authentic, scientific information and sound, practical application.

PROXIMATE COMPOSITION OF AMERICAN FOOD MATERIALS. *25c. 90 pages. U. S. Government Printing Office, Washington 25, D. C., 1948. Catalog No. A1.4/2:549.*

A FRUIT AND VEGETABLE BUYING GUIDE FOR CONSUMERS. *15c. 61 pages. U. S. Government Printing Office, Washington 25, D. C., 1948. Catalog No. A1.77:21.*

MEAT FOR THRIFTY MEALS. *15c. 46 pages. Illustrated. U. S. Government Printing Office, Washington 25, D. C., 1942. Catalog No. A1.9:1908.*

FAMILY FARE—FOOD MANAGEMENT AND RECIPES. *25c. 96 pages. Illustrated. U. S. Government Printing Office, Washington 25, D. C., 1950. Catalog No. A1.77:1/2.*

MONEY-SAVING MAIN DISHES. *15c. U. S. Government Printing Office, Washington 25, D. C., 1948. Catalog No. A1.35:289.*

FOOD FOR FAMILIES WITH SCHOOL CHILDREN. *10c. 23 pages. Illustrated. U. S. Government Printing Office, Washington 25, D. C., 1951. Catalog No. A1.77:13.*

HELPING FAMILIES PLAN FOOD BUDGETS. *15c. 16 pages. U. S. Government Printing Office, Washington 25, D. C., Revised 1952. Catalog No. A1.38:662/4.*

FOOD GUIDE FOR OLDER FOLKS. *5c. 16 pages. Illustrated. U. S. Government Printing Office, Washington 25, D. C., 1952. Catalog No. A1.77:17.*

IMPORTANCE OF NUTRITION TO GOOD HEALTH. *Health information series No. 31 (Public Health Service Publication No. 162) 1952. 12 pages. Illustrated. 5c. $3.75 per 100.*

The publications listed above are among many similar booklets and pamphlets issued by the U. S. Government Printing Office, dealing with food and nutrition. Prepared by home economists and dietitians, they present, in a style understandable to the layman, basic facts about food selection and preparation which should help insure good nutrition. Physicians may find that certain of their patients will be interested in securing such authoritative information inexpensively.

While not prepared with the diabetic in mind they contain much useful help for diabetic patients in purchasing and preparing their own meals, as in the booklets on fruit and vegetable buying and meat selection. Their emphasis, however, is on the normal family diet.

The well-known booklet on "Proximate Composition of American Food Materials" presents an analysis of a great variety of foods and includes a listing of fruits and vegetables classified as to their carbohydrate content. Information on the constituents of the edible portion of the many foods named in this valuable booklet is of great reference value not only to doctors but to dietitians and patients. It should be pointed out, however, that the data vary in certain respects from the figures for *available* carbohydrate, protein, and fat in the food exchange lists presented in the American Diabetes Association's "Diabetes Guidebook for the Physician" and in other recent publications.

MEMENTO DU DIABETIQUE. *Réservé aux Membres de l'Association Française des Diabétiques, Hôpital de la Pitié, 83 Bd. de l'Hôpital, Paris 13, France. pp. 42*

The French Association of Diabetics furnishes its members with this brochure, which resembles the books for patients, popular in this country. Diabetics and friends of diabetics in France are invited to join this Association, organized to protect their interests and to provide them with helpful information including, in addition to this booklet, a quarterly bulletin. The minimum annual dues for active members are 200 francs. Subscribing members and "bienfaiteurs" pay a minimum of 400 francs and 1000 francs, respectively.

The contents include a discussion of the symptoms of diabetes, diet and insulin, acidosis and other special problems occurring in the course of diabetes. Tables of food values are included; one section gives equivalents of 100 gm. of potatoes.

Emphasis is placed on regularity of medical supervision. The book closes with the following declaration: "The diabetic ought to take care of himself; his efforts will be rewarded. The diabetic can and ought to live a normal life: the American Davis Cup champions prove it! The diabetic who takes care of himself correctly can avoid complications. The medal of E. Joslin crowns this victory. At last, the life expectancy of the diabetic equals that of the normal person. Examined regularly every three months, he has even more chance of avoiding illness than the careless nondiabetic."

PROGRAM OF THE 13TH ANNUAL MEETING OF THE AMERICAN DIABETES ASSOCIATION MAY 30-31, HOTEL COMMODORE, NEW YORK CITY

In addition to the Scientific Sessions, details of which are given below, the schedule of events of the 13th Annual Meeting of the American Diabetes Association includes the following occasions:

Registration: May 30-31, 8:30 a.m.—5:30 p.m., Grand Ballroom Foyer.

Social Hour: Saturday, May 30, 6:30 p.m., South Room.

Banquet: Saturday, May 30, 7:15 p.m. Century Room.

Annual Business Meeting: Sunday, May 31, 2:00 p.m., East Ballroom.

Conference of Delegates of the Affiliate Associations: Monday, June 1, 2:00 p.m., West Ballroom.

Public Meeting, Sponsored by the Lay Society of the New York Diabetes Association and the American Diabetes Association: Monday, June 1, 8:15 p.m., Century Room.

At the Banquet on Saturday, May 30, Frank N. Allan, M.D., President of the American Diabetes Association, will speak on "Psychology of Diabetes". The Banting Memorial Medal will be presented to Shields Warren, M.D., Professor of Pathology, Harvard Medical School, Boston. Doctor Warren will deliver remarks on "Atomic Energy in Relation to Medicine". The Banting Medal will also be presented to Doctors Walter R. Campbell and Almon Fletcher, of the University of Toronto, Faculty of Medicine, by Dr. Charles H. Best.

There will be special presentations for outstanding contributions to the American Diabetes Association to Deaconess Maude Behrman, Mr. Fred Allen, and Mr. William F. Talbert.

SCIENTIFIC SESSIONS

Saturday, May 30, 2:00 P.M.

Joint Meeting with The Endocrine Society
Grand Ballroom

FRANK N. ALLAN and PAUL STARR, Presiding

Growth Hormone as an Anti-insulin Factor
RICHARD C. DE BODO, New York University College of Medicine, New York, N. Y.

Metabolic Effects of Crystalline Growth Hormone (Somatotrophin) in Man
EPHRAIM SHORR (by invitation), ANNE C. CARTER (by invitation), B. J. KENNEDY and RICHMOND W. SMITH, JR. (by invitation), New York Hospital, New York, N. Y.

Discussion of both of the above papers opened by FRANCIS D. W. LUKENS, University of Pennsylvania School of Medicine, Philadelphia, Pa., and LAURANCE W. KINSELL, University of California Medical School, San Francisco, Calif.

BANTING MEMORIAL LECTURE

An Interpretation of Diabetes in Light of Its Pathology

SHIELDS WARREN (by invitation), Professor of Pathology, Harvard Medical School, Boston, Mass.

Effect of Cortisone on Carbohydrate Metabolism, Measured by the Glucose Assimilation Coefficient

P. A. BASTENIE (by invitation), J. R. M. FRANCKSON (by invitation), and V. CONRAD (by invitation), introduced by E. H. RYNEARSON, Mayo Clinic, Rochester, Minn.

The Serum Polysaccharides in Diabetic Patients With and Without Degenerative Vascular Disease

HAROLD RIFKIN, JAMES BERKMAN (by invitation), and GEORGE ROSS (by invitation), Montefiore Hospital, New York, N. Y.

Discussion opened by HOWARD F. ROOT, New England Deaconess Hospital, Boston, Mass.

Studies in Experimental Diabetic Acidosis: Comparison of the Effect of Fructose and Glucose in the Initial Hours of Treatment

MAX MILLER, J. R. MURPHY (by invitation), J. W. CRAIG (by invitation) and HIRAM WOODWARD, JR., (by invitation), Western Reserve University School of Medicine, Cleveland, Ohio

Discussion opened by HENRY DOLGER, The Mount Sinai Hospital, New York, N. Y.

Spontaneous Diabetes in Dogs: An Account of Eight Cases

HENRY T. RICKETTS, University of Chicago, The School of Medicine, Chicago, Ill.

Discussion opened by CHARLES H. BEST, University of Toronto Faculty of Medicine, Toronto, Canada

Sunday, May 31, 9:00 A.M.

East Ballroom

FRANK N. ALLAN, Presiding

Renal Vascular Lesions in Diabetes Mellitus

E. T. BELL, University of Minnesota Medical School, Minneapolis, Minn.

Discussion opened by SHIELDS WARREN (by invitation), Harvard Medical School, Boston, Mass.

Pharmacologic and Clinical Studies on Two New Types of Long-Acting Insulins With Special Reference to Zinc Insulin Preparations (Novo). A Preliminary Report.

JOSEPH L. IZZO, with the assistance of ALFREDA M. GABIGA (by invitation), and JOANNE HOFFMASTER (by invitation), University of Rochester School of Medicine and Dentistry and Strong Memorial Hospital, Rochester, N. Y.

Discussion opened by FRANKLIN B. PECK, Indianapolis General Hospital, Indianapolis, Indiana

An Approach to the Quantitative Measurement of the Response to Insulin

LOUIS K. ALPERT and ALVIN E. PARRISH, George Washington University School of Medicine and the Veterans Administration Hospital, Washington, D. C.

Discussion opened by HENRY T. RICKETTS, University of Chicago, The School of Medicine, Chicago, Ill.

Studies with Radioactive Insulin

NEIL J. ELGEE (by invitation), ROBERT H. WILLIAMS, NORMAN D. LEE (by invitation), THOMAS WONG (by invitation) and JOHN R. HOGNESS (by invitation), University of Washington School of Medicine, Seattle, Wash.

Discussion opened by PETER H. FORSHAM, University of California Medical School, San Francisco, Calif.

Adrenal Cortical Function and the Blood Pyruvate and Lactate Response in Man

THOMAS F. FRAWLEY, JUAN J. PAULLADA (by invitation), and RAUL D. ALFARO (by invitation), Albany Medical College and the Metabolic Clinic, Albany Hospital, Albany, N. Y.

Discussion opened by KENDALL EMERSON, JR., Harvard Medical School, Boston, Mass.

Report of Follow-Up Survey of Individuals Found to Have Positive Screening Urine Tests in a Diabetes Detection Drive

SAMUEL D. LOUBE and LOUIS K. ALPERT (with the technical assistance of DOROTHY W. QUEEN, A.B.), George Washington University School of Medicine, Washington, D. C.

Discussion opened by HUGH L. C. WILKERSON, U. S. Public Health Service, Boston, Mass.

Disappearance of Hypercholesterolemia and Hyperphospholipidemia in Diabetic and Non-Diabetic Subjects During the Intake of Diets Containing Large Amounts of Vegetable Fat and Relatively Large Quantities of Protein

LAURANCE W. KINSELL, GILBERT C. COCHRANE (by invitation), JOHN W. PARTRIDGE (by invitation), JOHN P. JAHN (by invitation), HARRY E. BALCH (by invitation) and GEORGE D. MICHAELS (by invitation), Institute for Metabolic Research, Highland Alameda County Hospital, Oakland, Calif.

Discussion opened by HOWARD A. EDER (by invitation), Cornell University Medical College, New York, N. Y.

Glucose Tolerance in Hypertension and Obesity

MORRIS L. DRAZIN (by invitation), Veterans Administration, New York, N. Y.

Discussion opened by ALEXANDER MARBLE, Harvard Medical School, Boston, Mass.

Vascular and Hemodynamic Changes in the Smaller Blood Vessels of Diabetics and Prediabetics

JORN DITZEL (by invitation), New England Deaconess Hospital, Boston, Mass.

Discussion opened by WILLIAM P. BEETHAM (by invitation), New England Deaconess Hospital, Boston, Mass.

Effect of Purified Hyperglycemic-Glycogenolytic Factor (HGF, Glukagon) On Carbohydrate and Corticoid Metabolism in Normal and Diabetic Subjects

W. R. KIRTLEY, S. O. WAIFE and O. M. HELMER (by invitation), The Lilly Research Laboratories and the Indianapolis General Hospital, Indianapolis, Indiana

Discussion opened by I. J. PINCUS, Jefferson Medical College of Philadelphia, Philadelphia, Pa.

PANEL DISCUSSION — 12:00 Noon

The Clinical Use of Insulin

ARTHUR R. COLWELL, Moderator, Northwestern University Medical School, Chicago, Ill.

GARFIELD G. DUNCAN, Jefferson Medical College of Philadelphia, Philadelphia, Pa.

ROBERT L. JACKSON, Children's Hospital, Iowa City, Iowa

ALEXANDER MARBLE, New England Deaconess Hospital, Boston, Mass.

FRANKLIN B. PECK, Indianapolis General Hospital, Indianapolis, Indiana

DONALD S. SEARLE, Burroughs Wellcome & Company, Inc., Tuckahoe, N. Y.

SCIENTIFIC SESSION

Sunday, May 31, 2:30 P.M.

East Ballroom

RANDALL G. SPRAGUE, Presiding

Clinical Advantages of Crude Tests for the Degree of Ketonemia in Early Diagnosis of and Treatment for Diabetic Coma

GARFIELD G. DUNCAN, Jefferson Medical College of Philadelphia, Philadelphia, Pa.

Discussion opened by LEO P. KRALL, U. S. Public Health Service Hospital, Norfolk, Va.

Changes of Tissue Electrolytes in Diabetic Acidosis

HARVEY C. KNOWLES, JR., and GEORGE M. GUEST, University of Cincinnati College of Medicine and the Children's Hospital Research Foundation, Cincinnati, Ohio

Discussion opened by THOMAS H. McGAVACK, New York Medical College, New York, N. Y.

Some Observations on the Role of NPH Insulin in Children

H. W. BAIN and A. LAWRENCE CHUTE, University of Toronto Faculty of Medicine, Toronto, Canada

Discussion opened by PRISCILLA WHITE, Joslin Clinic, Boston, Mass.

Insulin and Nutritional Requirements of Children with Diabetes Mellitus in Good Control

P. TIRUMALA RAO (by invitation) and ROBERT L. JACKSON, Children's Hospital, Iowa City, Iowa

Discussion opened by G. A. Wrenshall (by invitation), University of Toronto Faculty of Medicine, Toronto, Canada

The Type of Diabetes Mellitus Associated with Diabetic Retinitis

GEORGE W. DANA, The Johns Hopkins Hospital, Baltimore, Md.

Discussion opened by JOSEPH H. BARACH, University of Pittsburgh School of Medicine, Pittsburgh, Pa.

PANEL DISCUSSION — 4:00 P.M.

What It Means to Live with Diabetes

FREDERICK W. WILLIAMS, Moderator, New York College of Medicine, New York, N. Y.

INGEBORG K. HINCK (by invitation), Yale University, New Haven, Conn.

PETER H. FORSHAM, University of California Medical Center, San Francisco, Calif.

NORMAN H. JOLLIFFE, New York City Department of Health, New York, N. Y.

LEON S. SMELO, Medical Diagnostic Clinic, Birmingham, Ala.

RANDALL G. SPRAGUE, Mayo Clinic, Rochester, Minn.

BY TITLE

The Relation of Potassium to Steroid-Hormone-Induced Insulin Resistance in Diabetic Patients

LAURANCE W. KINSELL, HARRY E. BALCH (by invitation), and GEORGE D. MICHAELS (by invitation), Institute for Metabolic Research, Highland Alameda County Hospital, Oakland. Calif.

Observations of the Effect of Heparin Therapy in Diabetic Glomerulosclerosis and Necrobiosis Lipoidica Diabeticorum

HYMAN ENGELBERG, (by invitation), University of California Medical School, San Francisco, Calif.

Cortisone Therapy in a Patient with Severe Spontaneous Hypoglycemia Followed for a period of one year and a half

H. E. GERSHBERG (by invitation) and ELAINE P. RALLI, New York University College of Medicine, New York, N. Y.

Complications of the Therapy of Diabetic Coma

J. WEISSBERG (by invitation) and THOMAS H. McGAVACK, New York Medical College, New York, N. Y.

Serum Lipids in Control and Diabetic Rats Fed Normal and High Fat Diets

R. N. CAGAN and LEO LOEWE (by invitation) Brooklyn Jewish Hospital, Brooklyn, N. Y.

Incidence of Diabetes in Pancreatic Disease

CHARLES R. TITTLE, JR., Abington, Pa.

Treatment of Diabetic Gangrene

SAUL S. SAMUELS, New York, N. Y.

Serial Plasma Acetone Guidance in the Treatment of Diabetic Coma

LEO P. KRALL and R. K. MADDOCK (by invitation) U. S. Public Health Service Hospital, Norfolk, Va.

The Relationship of Femoral Neuropathy to Diabetes Mellitus

JOSEPH I. GOODMAN, Cleveland Heights, Ohio

Psychological Problems in the Management of Diabetic Children

W. A. HAWKE (by invitation) and MARY EDDIS (by invitation) Toronto, Canada

Intravenous Fructose in Diabetes Mellitus: Advantages over Glucose in the Treatment of Diabetic Emergencies

HENRY DOLGER, S. KUPFER (by invitation), J. J. BOOKMAN (by invitation) and J. CARR (by invitation), The Mount Sinai Hospital, New York, N. Y.

The Mechanism of Diuresis in Diabetic Acidosis

HARVEY C. KNOWLES, JR., University of Cincinnati College of Medicine, Cincinnati, Ohio

Anticholinergic Drug Effect on Insulin Sensitivity in Diabetes

JAMES T. WORTHAM, J. L. FOSTER (by invitation), A. KAHN, JR., (by invitation), W. H. PERKINS (by invitation) and B. B. WELLS (by invitation), University of Arkansas School of Medicine, Little Rock, Ark.

Early Observations following Bilateral Adrenalectomy in a Young Diabetic with Advanced Arteriolar Disease

JAMES T. WORTHAM, J. W. HEADSTREAM (by invitation), B. B. WELLS (by invitation), W. H. PERKINS (by invitation), University of Arkansas School of Medicine, Little Rock, Ark.

Insulin and Fat of Human Pancreas

G. A. WRENSHALL (by invitation) and JEAN M. PATTERSON (by invitation), University of Toronto Faculty of Medicine, Toronto, Canada

The Interim Council Meeting Of The American Diabetes Association January 17-18, 1953

Toronto, Canada was chosen for the 1953 Interim Meeting of the Association's Council. Councilors present were: Doctors Frank N. Allan, George E. Anderson, Charles H. Best, Edward L. Bortz, Andrew L. Chute, Arthur R. Colwell, George M. Guest, Blair Holcomb, Robert L. Jackson, Alexander Marble, E. Perry McCullagh, Henry B. Mulholland, William H. Olmsted, Herbert Pollack, John A. Reed, Henry T. Ricketts, Edwin L. Rippy, Howard F. Root, Randall G. Sprague, Cecil Striker, George C. Thosteson, John H. Warvel, and Frederick W. Williams.

Although much of the work of the Council dealt with routine management of the affairs of the Association, a number of outstanding accomplishments and problems were discussed.

A revision of the Constitution and By-Laws of the Association was submitted by the Committee on Constitution, under the Chairmanship of Dr. Henry T. Ricketts; it will be presented for final action at the Annual Meeting in May, 1953. This revision has been needed for years. The new proposals will broaden the base of membership. They state more clearly our aims and purposes and provide a sound legal basis for our operations.

The Editor of DIABETES, Dr. Frank N. Allan, and the Chairman of the Editorial Board, Dr. Charles H. Best, presented a review of the first year's publication.

Dr. Frederick W. Williams, the Editor in Chief of the A.D.A. FORECAST, submitted a report concerning this publication. There are over 21,000 subscribers and it is now on a sound financial basis. Doctors William H. Olmsted, Priscilla White and S. Gordon Ross were appointed to the Editorial Advisory Board for a term of three years.

Acting on the recommendation of the Committee on Finance, chaired by Dr. Cecil Striker, the Council voted approval of a decision to invite diabetics, through an appeal in the FORECAST, to contribute to the American Diabetes Association in support of its educational and research projects.

The Committee on Membership presented an interest-

ing analysis of our membership. It was announced that the new directory of membership will be ready for distribution in the near future. It was further announced that the history of our Association would be brought up to date and published. Dr. William Muhlberg, one of the founders of the A.D.A. and first Treasurer, was elected to honorary membership, a recognition long past due.

The Council discussed at length plans for the reorganization of the affiliate structure and its relationship to the Association. After much deliberation the matter was referred to a Committee on Policies which will report at the May Meeting.

Doctors Edward S. Dillon and Herbert Pollack together with Mr. J. Richard Connelly, the Executive Director, were appointed Delegates to the National Health Council, and Dr. Edward L. Bortz was named as a Nominee to serve on the Board of Directors of the National Health Council.

A report of the first Postgraduate Course was presented by Dr. Edward L. Bortz, Chairman of the Committee on Postgraduate Education. It was apparent that the Course would be successful and attendance would exceed all expectations. Many applications were rejected with regret because of limited facilities, but those who were not able to attend this year would be given priority for future courses. The Council voted commendation of Doctor Bortz and his committee for the success of this new undertaking.

The Council voted that the American Diabetes Association should become a member of the International Diabetes Federation, with the provisos that the I.D.F. Constitution and By-Laws be ratified by the constituent member organizations and that any further changes in the proposed Constitution and By-Laws of the Federation be submitted to our Association's Executive Committee for final approval. The relationship will undoubtedly permit mutually valuable assistance and such closer ties should bring much helpful service to the diabetic in the future.

The question of the time and place of our Annual Meeting is a perennial subject for discussion. The Council reports that because of the great service our organization renders to the general practitioner, it felt that the Annual Meeting should precede and be at the same place as the meeting of the American Medical Association.

Many splendid committee reports were submitted, but the availablity of space precludes their full publication. I would, however, like to mention, especially, the splendid contribution of the Committee on Camps presented by Dr. Alexander Marble; the Committee on Information for Diabetics presented by Dr. Herbert Pollack; and the Committee on Food and Nutrition by Dr. William H. Olmsted.

JOHN A. REED, M.D., *Secretary*

ASSOCIATION NEWS

THIRTEENTH ANNUAL MEETING, MAY 30-31, 1953 HOTEL COMMODORE, NEW YORK CITY

As this issue goes to press plans are being completed for the forthcoming Annual Meeting which is expected to be the largest one held by our Association to date.

A copy of the Preliminary Program has been mailed to each member, it also appears in the Organization Section of this issue. We would particularly like to call your attention to the Scientific Sessions. In addition to the excellent individual papers, the two Panels scheduled for Sunday, May 31, should prove highly interesting and informative.

Announcement of the awarding of the Banting Medal to Shields Warren, M.D., who will present the Banting Memorial Lecture Saturday afternoon, and to Doctors Walter R. Campbell and Almon Fletcher of Toronto, Canada, who were the first to use insulin clinically, was made in the previous issue of DIABETES.

The Banquet will include not heretofore announced special presentations to Deaconess Maude Behrman, consulting dietitian to the A.D.A. FORECAST, and Messrs. Fred Allen and Bill Talbert for their generous and unselfish participation in Diabetes Detection Drives.

Members who have not made their reservations at the Hotel Commodore are urged to do so immediately. If a member has mislaid the hotel reservation card, a duplicate may be secured from the National Office. Banquet tickets are available at $6.75 each.

DISPLAY OF SCIENTIFIC EXHIBIT

The Association's exhibit "Vascular Complications of Diabetes" will be displayed in the Scientific Exhibits section at Grand Central Palace, Space No. 506, (Fourth Floor) at the American Medical Association's Annual Meeting, June 1-5.

All members, especially those who have not seen this effectively presented exhibit, are cordially invited to visit the display.

CLINCAL CENTER OF THE NATIONAL INSTITUTES OF HEALTH

The opening of the 500-bed Clinical Center at Bethesda, Maryland, scheduled for this spring, has been delayed until about July 15. According to reports, occupancy will be only about 50 per cent in the first year of operation.

The National Institute of Arthritis and Metabolic Diseases has been assigned approximately 78 beds of the total for selected cases, 25 of which will be allocated for arthritis. The remaining 53 beds assigned to that Institute will be used for the study of diabetes and other metabolic diseases.

MILITARY SERVICE FOR DIABETIC PHYSICIANS

With the increasing scarcity of draft-available physicians, the Department of Defense will accept for military service, it is reported, physicians with diabetes whose ailment is under control.

Following the announcement made earlier in the year (see DIABETES January-February 1953, Vol. 2, No. 1.) the Association has been informed that a number of diabetic doctors have been reclassified 1-A.

1952 DIABETES DETECTION DRIVE REPORTS

The Chairman of the Committee on Detection and Education, Doctor John A. Reed, has made a special request that all Chairmen of Committees on Diabetes of County and State Medical Societies and Chairmen of Committees on Detection and Education of Affiliate Associations submit their 1952 reports as soon as possible.

THIRTY-FOURTH ANNUAL CONVOCATION OF THE AMERICAN COLLEGE OF PHYSICIANS

Charles H. Best, C.B.E., M.D., F.R.S., received the John Phillips Memorial Award of The American College of Physicians for outstanding achievement in internal medicine at its 34th Annual Convocation in Atlantic City,

N.J., April 15, 1953. Doctor Best delivered the John Phillips Memorial Lecture on "The Action of Insulin".

Hilton S. Read, M.D., of Atlantic City, was General Chairman of the Committee on Arrangements for the session, and Doctor Edward L. Bortz, a Regent of the College, served as a member of the Committee on Clinical Pathological Conferences. One of the conferences was moderated by Doctor James A. Greene of Houston, in which Doctor Bortz was a participant.

Doctors Christopher J. McLoughlin and Lester M. Petrie, of Atlanta, Georgia, presented a paper entitled "Blood Sugar Metabolism in Adults in Georgia". The paper was discussed by Doctor Hugh L. C. Wilkerson, of Boston.

Other members of the Association who presented papers were George W. Thorn, M.D., of Boston, "Recent Studies on ACTH and Cortisone"; Joseph T. Roberts, M.D., of Buffalo, "Unilateral Renal Ischemia ('Goldblatt Kidney') with Nephrectomy and Three-Year Cure of Malignant Hypertension"; Arthur C. Curtis, M.D., of Ann Arbor, Michigan, "The Deep Mycoses".

Members who participated as panelists were: Frank N. Allan, M.D., of Boston; Edward L. Bortz, M.D., David A. Cooper, M.D., Garfield G. Duncan, M.D., and Joseph R. Elkington, M.D., of Philadelphia; Edgar S. Gordon, M.D., of Madison, Wisconsin; James A. Greene, M.D., of Houston; Lawrence E. Hinkle, Jr., M.D., of New York; Francis D. W. Lukens, M.D., of Philadelphia; Gerald H. Pratt, M.D., of New York, and Priscilla White, M.D., of Boston.

DIABETES POSTGRADUATE COURSE HARVARD MEDICAL SCHOOL

A course entitled: "Diabetes and Endocrinology in Relation to General Medicine" is being offered as the fifth of a series of seven courses for graduates by the Harvard Medical School.

Scheduled for July 6-8, 1953, the course consists of clinical demonstrations and lectures presenting the fundamental physiology, pathology, chemistry and diagnosis and treatment of diabetes and related endocrine disorders, and will be directed by Howard F. Root, M.D., and Associates of the New England Deaconess Hospital. Applications should be sent to the Assistant Dean, Courses for Graduates, Harvard Medical School, Boston 15, Massachusetts.

THE UNIVERSITY OF VIRGINIA HOLDS CONFERENCE ON DIABETES

The School of Medicine of the University of Virginia conducted a "Conference on Diabetes and Its Complications", Friday, April 17, at Charlottesville. Members of the Association who participated in the all-day program are: Charles H. Best, M.D., "The Action of Insulin"; Arthur R. Colwell, M.D., "The Clinical Use of Insulin"; Henry B. Mulholland, M.D., "Office Management of Diabetes Mellitus"; Thomas S. Edwards, M.D., "Renal, Retinal and Neural Complications of Diabetes".

CLINICAL NEWS FROM AFFILIATE ASSOCIATIONS

Through expansion of the Affiliate Service Program of the American Diabetes Association, an increasing number of meetings and activities of clinical interest are being reported to the National Organization.

CONNECTICUT DIABETES ASSOCIATION: The Fifth Annual Meeting of the Connecticut Diabetes Association was held in conjunction with the Connecticut State Medical Society on April 28, in Hamden. Doctor Frederick W. Williams of New York City was the principal speaker.

LOS ANGELES DIABETES ASSOCIATION: The Annual Dinner Meeting was held on Wednesday, April 29, and John W. Gofman, M.D. delivered a paper on "The Relationship of Lipoproteins to Diabetes Mellitus". Doctor Gofman's paper was discussed by Doctors Hyman Engelberg and Willard J. Zinn.

NEW ENGLAND DIABETES ASSOCIATION: Doctor Edward L. Bortz, of Philadelphia, will read a paper entitled "Evaluation of Current Practices in the Control of Diabetes Mellitus" at the Annual Meeting of the New England Diabetes Association, Wednesday, May 13, at the Elliott P. Joslin Auditorium of the New England Deaconess Hospital. The meeting will be preceded by dinner at 6:30 o'clock at the Hotel Beaconsfield, Brookline.

NEW YORK DIABETES ASSOCIATION: The Clinical Society held an "Open Meeting on Diabetes Mellitus" on Wednesday evening, April 22, at the New York Academy of Medicine. The following papers were presented by the Jewish Sanitarium and Hospital for Chronic Diseases of Brooklyn: "Hypoglycemia Responsiveness", Sydney S. Lazarus, M.D. and Bruno W. Volk, M.D.; "Effect of Cobaltous Chloride on the Pancreatic Alpha Cells and on the Blood Sugar Level", Martin G. Goldner, M.D., Bruno W. Volk, M.D. and Sydney S. Lazarus, M.D. Maurice Drazin, M.D., of the Veterans Administration Regional Office, talked on "Glucose Tolerance in Hypertension and Obesity".

TEXAS DIABETES ASSOCIATION: Doctor Howard F. Root, of Boston, was the Guest Speaker at the Annual Meeting of the Texas Diabetes Association on April 26 in Houston. He presented a paper entitled "Prevention of Complications by Control of Diabetes".

Others who participated in the program are: Edwin L. Rippy, M.D., of Dallas, "Diabetic Problems in Childhood"; James A. Greene, M.D., of Houston, "The Mechanism of Utilization of Additional Carbohydrate Intake without Extra Insulin by Patients with Diabetes Mellitus"; H. T. Engelhardt, M.D., of Houston, "Observations on the Detection of Diabetes: A Method of Detecting Diabetes"; Raymond Gregory, M.D., of Galveston, "The Treatment of Diabetic Acidosis with and without Intravenously Administered Glucose; An Experimental Study"; Ralph G. Greenlee, M.D., of Temple, Texas, "Diabetic Neuropathy Treated with Pregnant Mammalian Liver Extract and Vitamin B12".

More than a hundred physicians and other scientists attended the meeting. It was announced that the Texas Diabetes Association had been active in the formation of the Houston Area Diabetes Association and plans are being made for the formation of an organization in Central Texas.

VIRGINIA DIABETES ASSOCIATION: On May 6, the Virginia Diabetes Association held its Annual Meeting at the Hotel Jefferson, Richmond. The program, which began at 9 A.M., included the following papers: "Management of the Obese Diabetic", Frank A. Wade, M.D. and H. St. George Tucker, M.D., Richmond; "Considerations of Kimmelstiel-Wilson Syndrome", James Hutcheson, M.D., Roanoke; "Choosing Insulin for the Diabetic", William R. Jordan, M.D., Richmond; "Common Errors in Therapy", H. B. Mulholland, M.D., Charlottesville; Panel Discussion on Therapy, Robert C. Crawford, M.D., Roanoke, William R. Jordan, M.D., Richmond, H. B. Mulholland, M.D., Charlottesville, George S. Grier, III, M.D., Newport News.

PERSONAL

The Commission on Chronic Illness announced that Henry B. Mulholland, M.D., of Charlottesville, Virginia, has been appointed as one of three members of a Commission to serve as an editorial board to develop reports of the Conference on Care of the Long-Term Patient, scheduled for some time in 1954.

Samuel Soskin, M.D., of Beverly Hills, California, addressed the Industrial Medical Association section of the 1953 Industrial Health Conference, on April 23, on the subject of "Diabetes—Its Relation to Industry".

Norman H. Jolliffe, M.D., of New York City, was re-elected President of the National Vitamin Foundation at its Annual Meeting held March 4 at the Biltmore Hotel, New York City.

NEW MEMBERS

As announced in the March-April (Vol. 2, No. 2) issue of DIABETES, the names of newly elected members to the Association will be published as often as practicable.

The following Active Members were elected as of April 15, 1953:

MICHAEL E. BRODSKY
Bridgeport, Conn.

THOMAS M. BROWN
Muncie, Indiana

JAMES F. D. CANTELON
Toronto, Canada

PETER D. COMANDURAS
Washington, D. C.

L. M. DEL VECCHIO
Reading, Pennsylvania

ALBERT E. DISKAN
Manchester, Conn.

DAVID L. ELLRICH
Westport, Conn.

FRANKLIN L. GEIGER
Columbia, South Carolina

RALPH GOLDMAN
Los Angeles, California

ARCHIE E. GROFF
Houston, Texas

JACQUES GRUNBLATT
North Creek, New York

BEN DAVID HALL
Honolulu, Hawaii

FRANKLIN G. HOFFMAN
Indianapolis, Indiana

JAMES W. HOOKER
Urbana, Illinois

JOHN G. HULL
Houston, Texas

STUART E. KROHN
Utica, New York

HAROLD J. LEHMUS
Manchester, Conn.

CHARLES M. LINDSAY
North Bend, Oregon

J. B. R. MCKENDRY
Ottawa, Canada

WILLIAM ST. G. METZLER
Toronto, Canada

WILLIAM S. MONTGOMERY
Newburgh, New York

EDWIN F. NECKERMAN
Elmhurst, Illinois

GEORGE W. PERDUE
Houston, Texas

RAYMOND V. RANDALL
Rochester, Minnesota

EDWIN ROBINS
Queens, New York

ROBERT R. ROCKLIN
Los Angeles, California

CLARE S. SANBORN
Windsor, Canada

SEYMOUR SIEGEL
Philadelphia, Pennsylvania

CARLOS DALE SPECK, JR.
Houston, Texas

JULES STAHL
Strasbourg, France

IRWIN STOVER
Toledo, Ohio

OLIVER E. TURNER
Pittsburgh, Pennsylvania

JOSEPH R. VAN DYNE
Forest Hills, New York

JAMES F. WALKER
Erie, Pennsylvania

CHARLES H. WHALEN
New Castle, Pennsylvania

ROBERT H. WILLIAMS
Seattle, Washington

FRANCIS LOUIS WIZA
Chicago, Illinois

EDWARD T. WOLF
Houston, Texas

AARON B. YASINOW
Cleveland, Ohio

ACTIVE MEMBERS ELECTED AS OF MAY 1, 1953:

MELVIN BACON
Sanford, Maine

JACK BRONFENBRENNER
Benton Harbor, Michigan

MARVIN B. DAY
Hartford, Connecticut

GEORGE R. DILLINGER
Thomasville, Georgia

JANINE L. DUCKERS
BRUSSELS, BELGIUM

HERBERT S. EVERETT
St. Stephen, N.B., Canada

RENE A. R. FRANCOIS
Lyon, France

DONALD W. GRESSLY
Beaver, Pennsylvania

ARNOLD L. HELLER
Cleveland, Ohio

EARL B. HOBBS
Smithville, Missouri

ANDREW J. JESACHER
Sarasota, Florida

HENRI LESTRADET
Paris, France

DONALD F. LEWIS
Medicine Hat, Alberta, C.

ROBERT F. LOEB
New York, New York

RAYMOND E. LOWE
Warren, Pennsylvania

MAURICE LUGITCH
Dorchester, Massachusetts

RICHARD V. MCKAY, JR.
Dubuque, Iowa

ALLEN P. NEWMAN
Fremont, Ohio

MARIE ORTMAYER
Chicago, Illinois

JULIEN PESANT
Montreal, Canada

WALTER S. PHARES
Rochester, Minnesota

THEODORE Z. POLLEY
Joliet, Illinois

SAMUEL B. REICH
Hackensack, New Jersey

JOSEPH A. RUSSO, JR.
Brooklyn, New York

F. FREDERICK RUZICKA
Baltimore, Maryland

MARIDEL SAUNDERS
New Orleans, Louisiana

ARMIN F. SCHICK
Chicago, Illinois

IRVING SOMACH
New York, New York

EUGENE J. STEINBERGER
Detroit, Michigan

HOWARD S. TRAISMAN
Chicago, Illinois

THEODORE F. TREUTING
New Orleans, Louisiana

WALTER G. UNGLAUB
New Orleans, Louisiana

CHARLES S. VIL
Chicago, Illinois

EDWARD B. WELLS
Erie, Pennsylvania

RUSSELL F. WIGGERS
Cincinnati, Ohio

ASSOCIATE MEMBERS ELECTED APRIL 15, 1953:

HEINRICH BARTELHEIMER
Berlin, Germany

JEAN I. TRENHOLME, R.N.
Montreal, Canada